Biosimilars - An Update
Focused on Quality Considerations

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Advisory Committee for Pharmaceutical Science and Clinical Pharmacology
August 8, 2012

Statute

- The Biologics Price Competition and Innovation Act (BPCI Act) was passed as part of healthcare reform (Affordable Care Act) that President Obama signed into law on March 23, 2010.
- The BPCI Act creates an ***abbreviated licensure pathway for biological products shown to be biosimilar to or interchangeable*** with an FDA-licensed reference product.

What is an Abbreviated Licensure Pathway for Biological Products?

- A biological product that is demonstrated to be "***highly similar***" to an FDA-licensed biological product (the ***reference product***) may rely on certain existing scientific knowledge about the safety, purity, and potency of the reference product.
- This new licensure pathway permits a "biosimilar" biological product to be licensed based on less than a full complement of product-specific nonclinical and clinical data.

Biosimilar Draft Guidances

Overarching Goal: *Efficient, predictable and transparent regulatory pathway*

1. Scientific Considerations in Demonstrating Biosimilarity to a Reference Product (Sci. Cons.)
2. Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009 (Q&A)
3. Quality Considerations in Demonstrating Biosimilarity to a Reference Protein Product (Quality)

Always consider entire text and context of guidance excerpts

Biosimilarity

- *Biosimilar* or *biosimilarity* means that "the biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components,"
- and that "there are no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity, and potency of the product

How close is close enough?

Speakers

- Quality Considerations for Biosimilars
  - *Marjorie Shapiro, Ph.D, Division of Monoclonal Antibodies/OBP/OPS/CDER/FDA*
- PhRMA Perspectives
  - *Robert J. Mattaliano, Ph.D., Group VP, Biologics Development, Genzyme Corporation*
- GPhA Perspectives
  - *Mark McCamish, MD, Ph.D. Global Head Biopharmaceutical Development, Sandoz International, GmbH*

Quality Considerations for Biosimilars

Marjorie Shapiro, Ph.D.
Division of Monoclonal Antibodies/OBP/OPS

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Definition of Biosimilar/Biosimilarity in BPCI Act

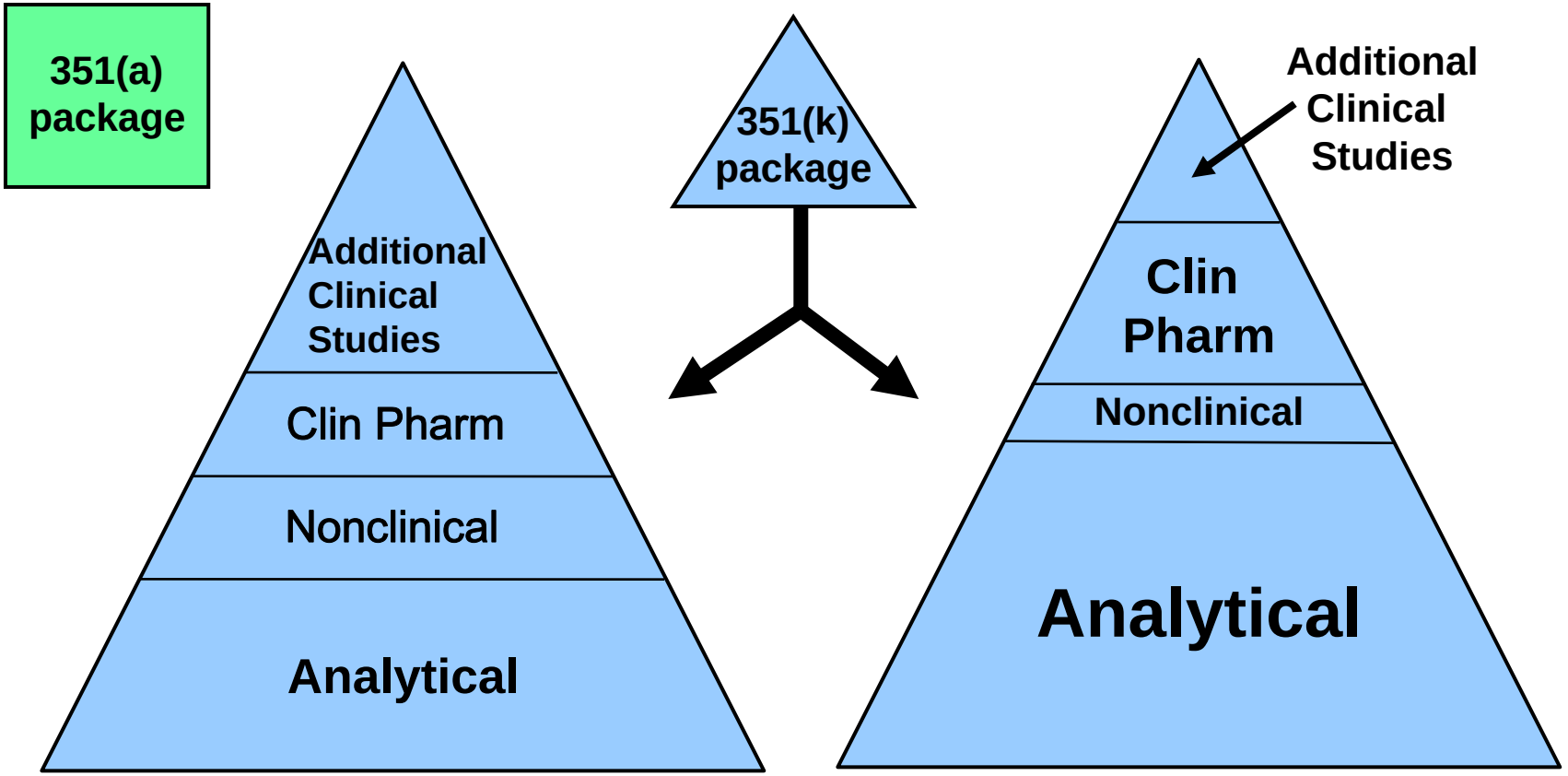
Biosimilar* or *biosimilarity is defined in Section 351 of the PHS Act to mean that "the biological product is **highly similar** to the reference product notwithstanding minor differences in clinically inactive components," and that "there are **no clinically meaningful differences** between the biological product and the reference product in terms of the safety, purity, and potency of the product".

Section 7002(b)(2) of the Affordable Care Act, amending section 351(i) of the PHS Act.

Scientific Considerations Draft Guidance

The stepwise approach should start with extensive structural and functional characterization of both the proposed product and the reference product, which serves as the **foundation** of a biosimilar development program.

Highly Similar Analytical and PK/PD Data = Lower Risk of Clinical Differences

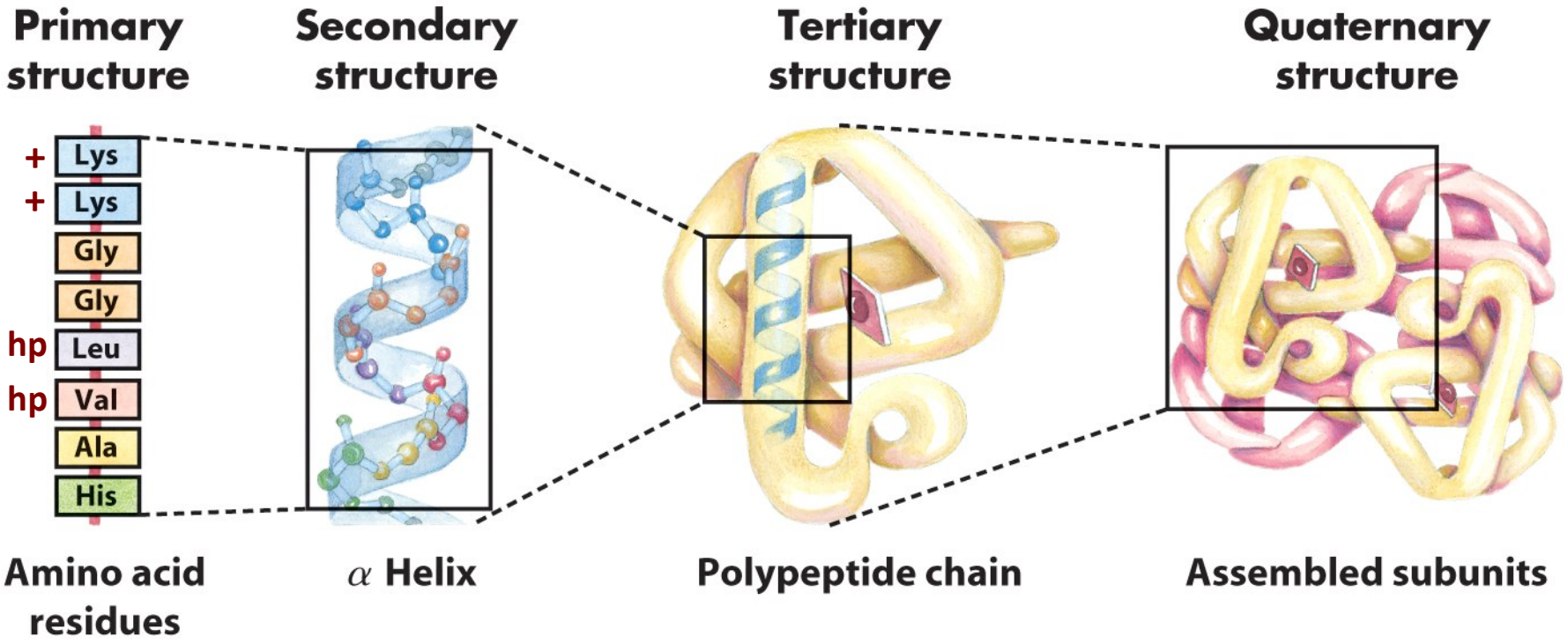


Two approaches to achieve biosimilarity

Quality Considerations Draft Guidance

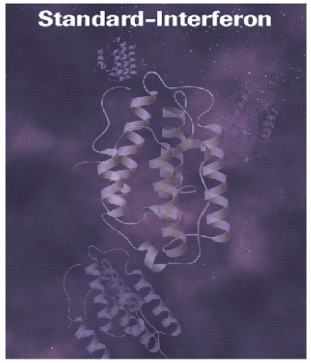
- Focuses on analytical studies that may be relevant to assessing the similarity between a proposed biosimilar protein product and a reference product.
- General principles:
  - Importance of extensive analytical, physicochemical and biological characterization
  - Product/process impurities, expression system
  - Identification of lots used in the various analyses for biosimilarity determination
  - Advances in manufacturing science and Quality-by-Design approaches may facilitate “fingerprint”-like analysis

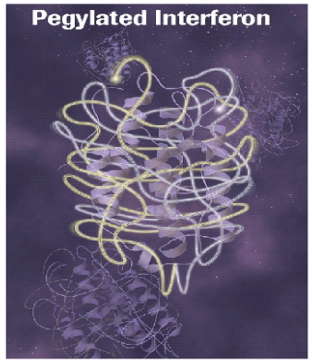
Hierarchy of Protein Structure



All need to be evaluated as part of analytical similarity studies

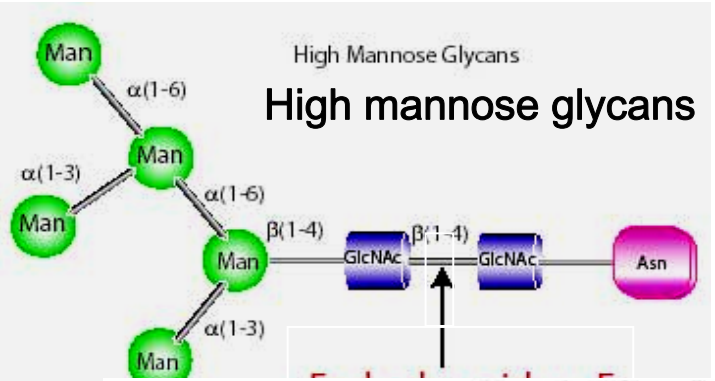
Protein Heterogeneity



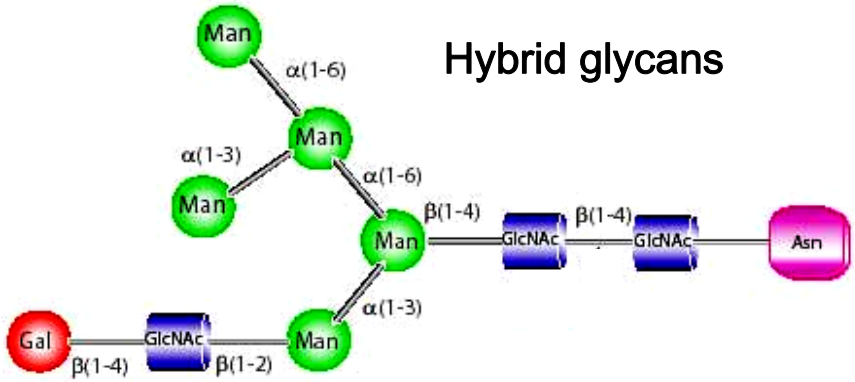


- Amino Acid Substitution
- N- and C-terminal mods
- Mismatched S-S bonds
- Folding
- Truncation
- Aggregation
- Multimer Dissociation
- Denaturation
- Acetylation
- Fatty acylation
- Deamidation
- Oxidation
- Carbamylation
- Carboxylation
- Formylation
- γ-Carboxyglutamylation
- O-linked Glycosylation
- N-linked Glycosylation
- Methylation
- Phosphorylation
- Sulphation
- PEGylation

Types of N-linked glycans



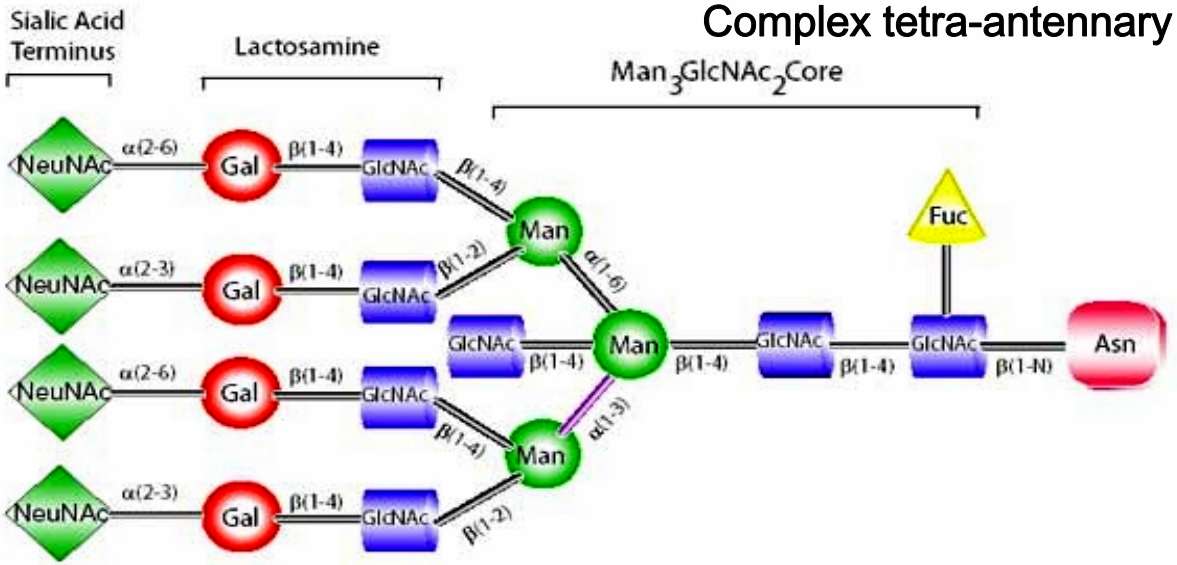
High mannose glycans



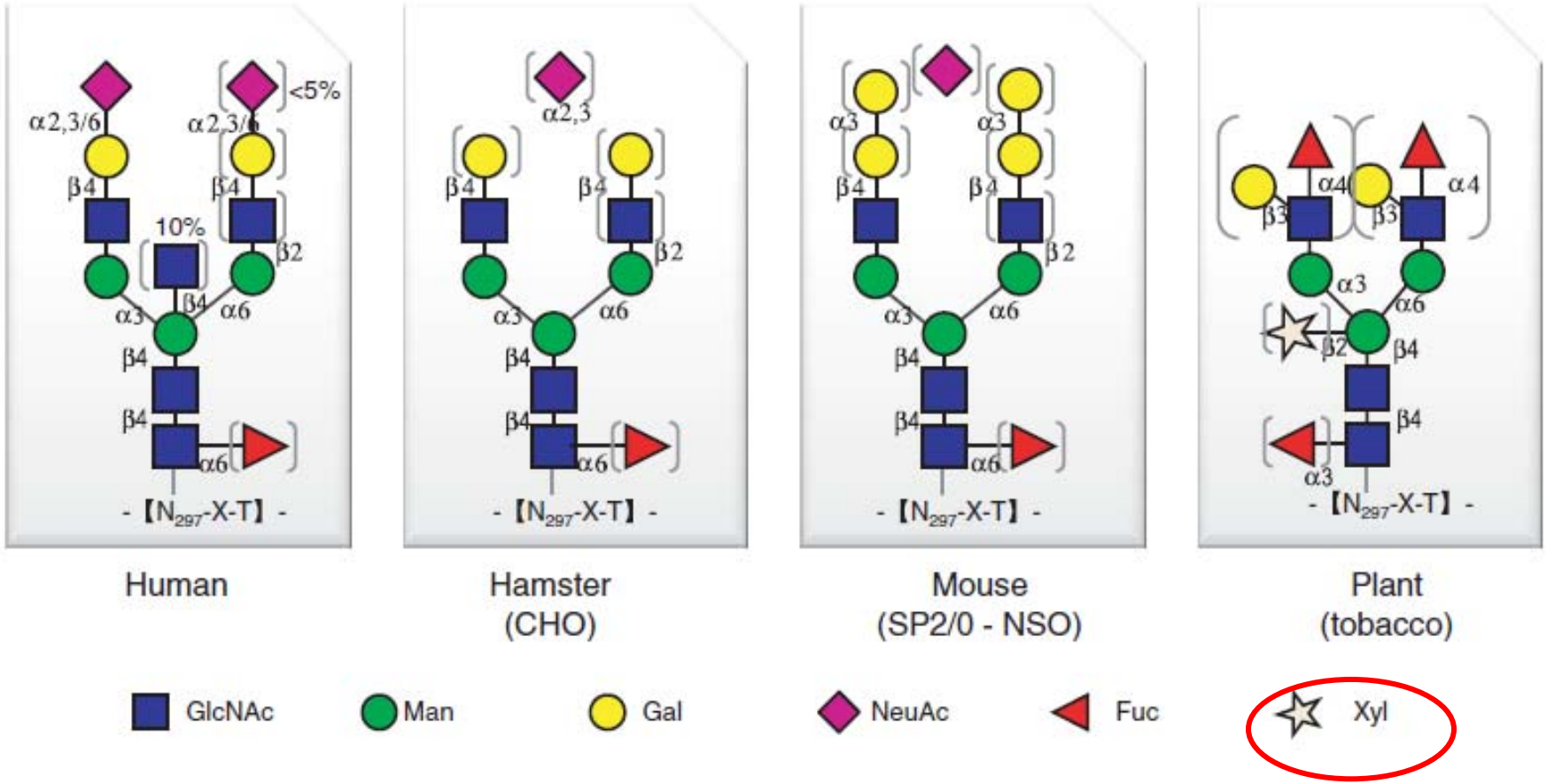
Hybrid glycans

Complex Tetraantennary Glycan

Complex tetra-antennary glycans



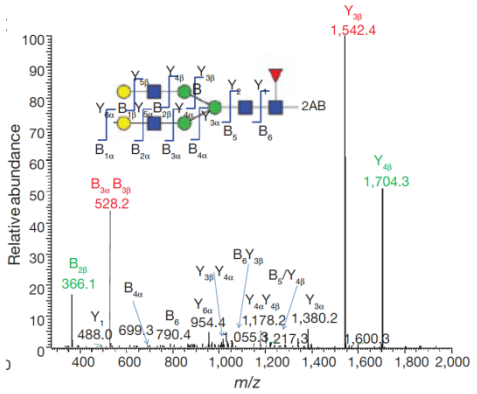
Antibody Glycans

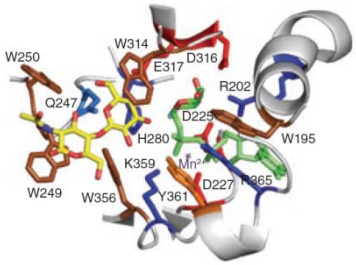


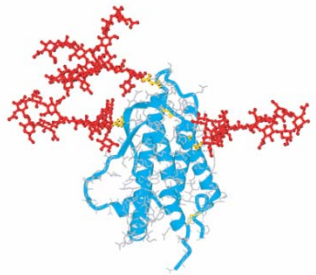
Gomord et al. Plant Biotechnology Journal 2010

Analytical Tools to Evaluate Proteins

- Amino acid sequence and modifications:
  - MS, peptide mapping, chromatographic separations
- Folding:
  - S-S bonding, calorimetry, HDX and ion mobility MS, NMR, dyes, circular dichroism, Fourier transform spectroscopy, fluorescence
- Subunit interactions:
  - Chromatography, ion mobility MS
- Heterogeneity of size, aggregates, charge, hydrophobicity:
  - Chromatography resins; gel & capillary electrophoresis, light scatter, IM-MS, Analytical ultracentrifugation, size-exclusion chromatography, field flow fractionation, light scatter, microscopy
- Glycosylation
  - Anion exchange, enzymatic digestion, peptide mapping, CE, MS
- Bioactivity
  - Cellular and animal bioassays; ligand & receptor binding (ELISA, surface plasmon resonance), signal transduction
- Impurities
  - Proteomics, immunoassays, metal & solvents analysis





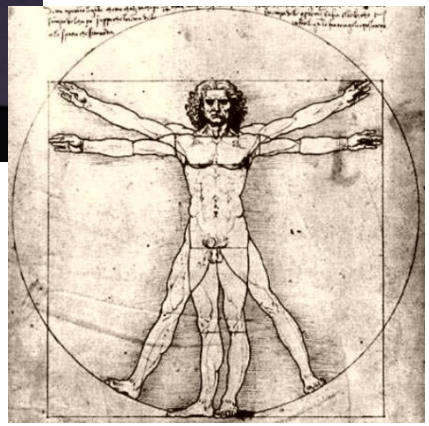


Choice of Analytics

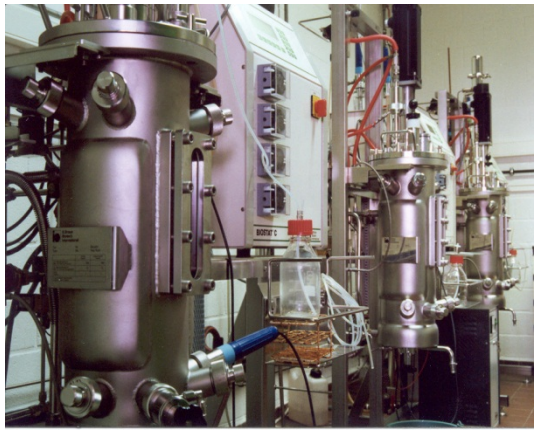
- It is expected that appropriate analytical test methods will be selected based on:
  - the nature of the protein being characterized,
  - knowledge regarding the structure, and
  - heterogeneity of the reference and proposed biosimilar product, including
    - » known and potential impurities, and
    - » characteristics that are critical to product performance
- Use of stability studies to reveal subtle or hidden differences

Source Materials

Mice

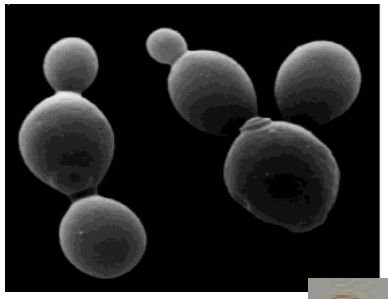


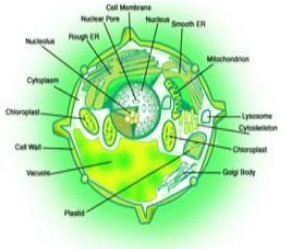
Humans



Mammalian cell-culture

Bacteria



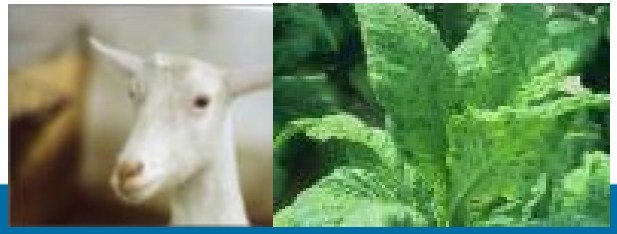


Plant cell-culture

Insect cell-culture

Yeast

Transgenics

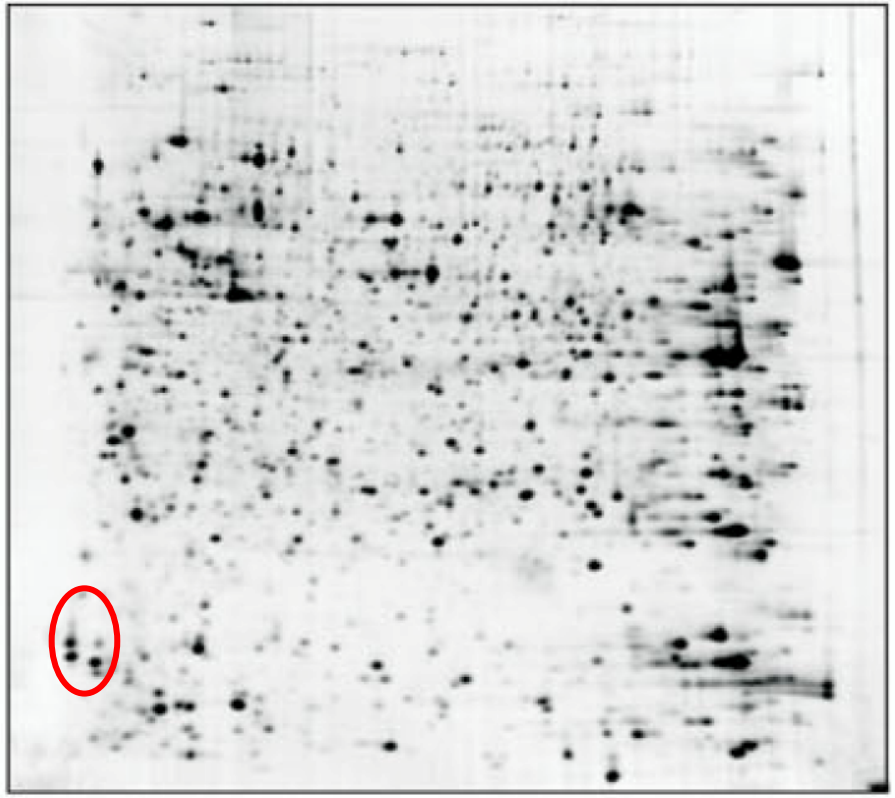


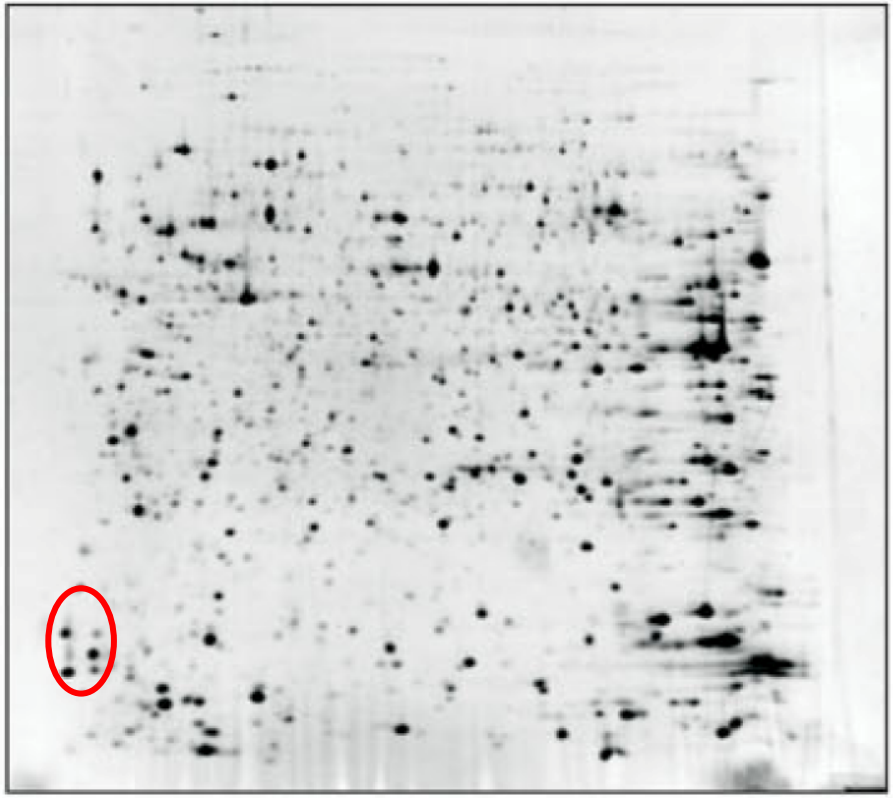
Expression Systems

- **Differences** between the chosen expression system of the proposed biosimilar product and that of the reference product should be carefully considered.

- The type of expression system and host cell will significantly affect the types of process- and product-related substances and impurities.

Protein Impurities – The *E. coli* Proteome





Host cell proteins can be detected, identified, and quantified.

Similar impurities profiles decrease risk of product difference.

Know Your Protein!

- Need to understand what is important for biological function of protein
- If multiple MOAs, need to understand MOA for specific indication and critical quality attributes for that MOA
- Need to understand impact of potential post translational modifications
  - Oxidation of met and deamidation of asn may impact function or immunogenicity of some proteins but not others
- Need to understand how combinations of quality attributes interact to impact clinical performance.
- Case-by-case evaluation of different post translational modifications and any potential clinical impact

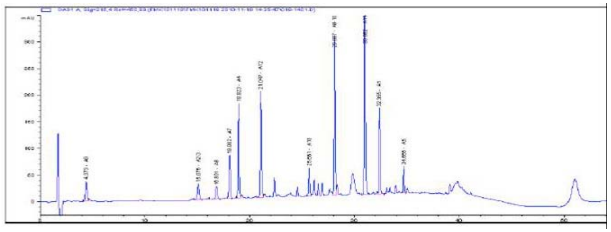
Approach to Reverse Engineering for Developing a Biosimilar Product

- Analyze cell substrates
  - Design so that host cell protein profile will match
- Reverse engineer upstream manufacturing
  - Media composition and fermentation parameters
  - Growth characteristics
  - Match product attributes
- Reverse engineer downstream purification
  - Match product variants and process impurities
- Formulation
  - Match stability profile

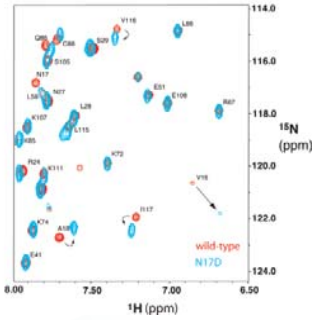
Fingerprinting

- It may be useful to compare products using a meaningful fingerprint-like analysis algorithm
  - that covers a large number of additional product attributes and their combinations with high sensitivity using orthogonal methods.
- Advances in manufacturing science and Quality-by-Design approaches may *allow a* better match to a reference product's fingerprint.
- May allow a more selective and targeted approach to subsequent animal and/or clinical studies.

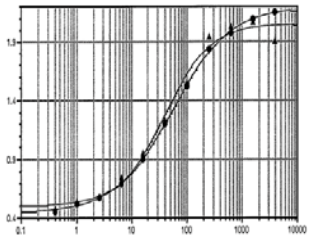
Fingerprinting



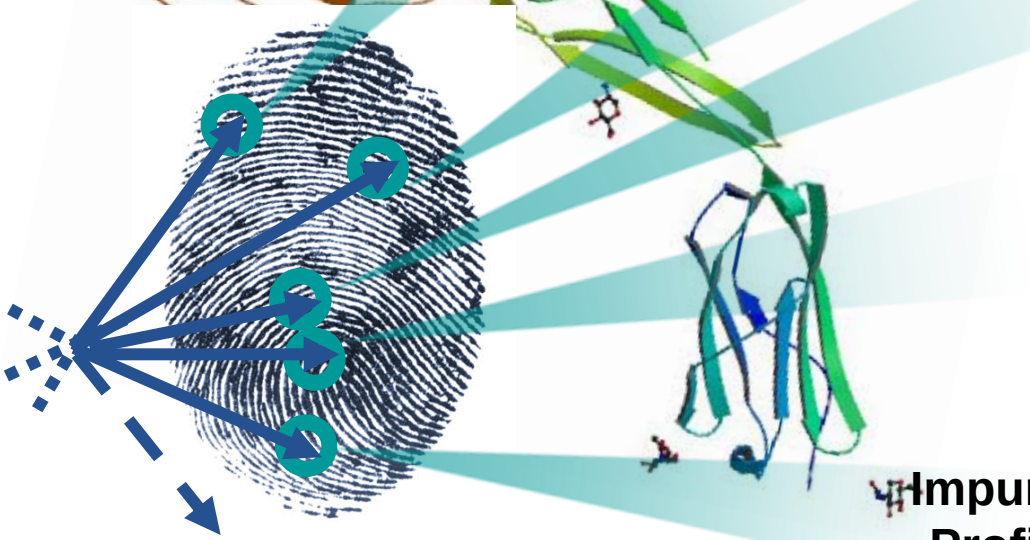
Sequence & Modifications

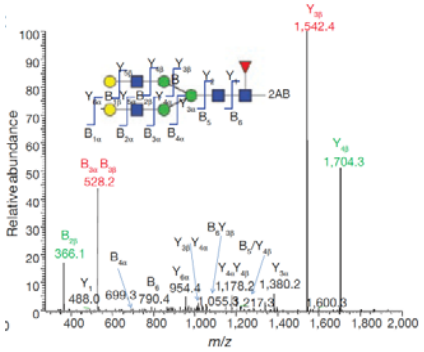


Higher Order Structure



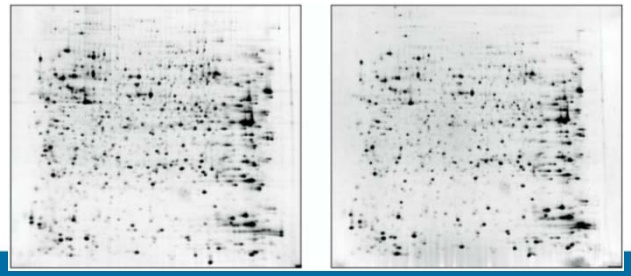
Bioactivity



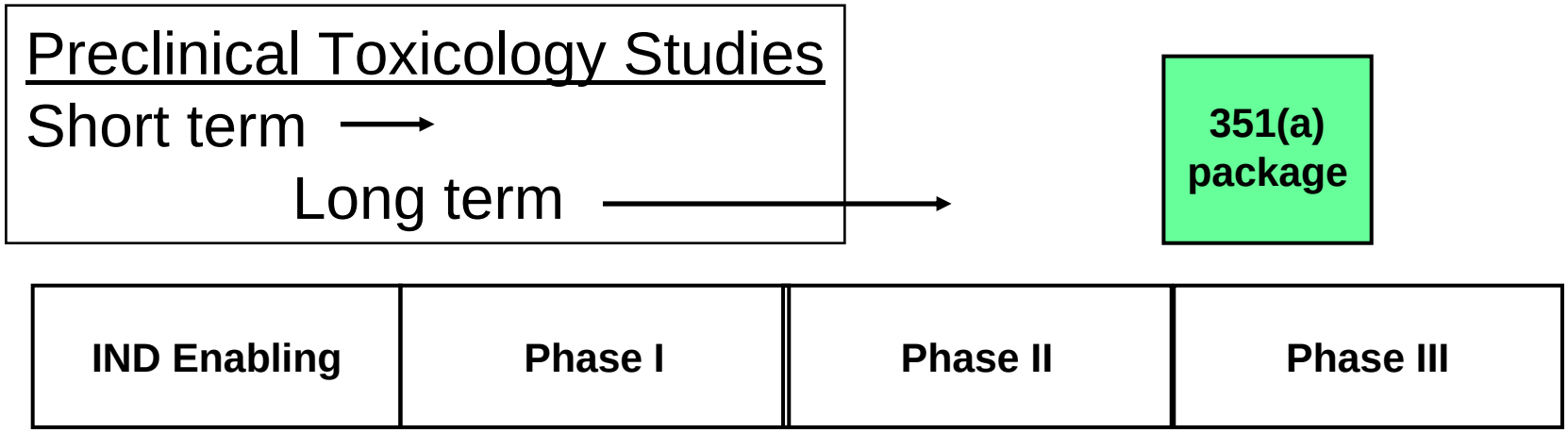


Glycoforms

Impurity Profile



Data Collection During New Biological Entity Product Development



Adapted from a slide by Tony Mire-Sluis

Product Quality Assays During New Biological Entity Product Development

Development Decision **IND** **BLA**

Research	Developmental Research	IND Enabling	Phase I II III	IV Post Marketing
Early purification studies	Protein selection	Limited Structural characterization	In depth characterization assay development	Lot release
Immuno-assay based lot release	Bioassay Development	Preliminary biological characterization	Validated Lot release assay development	Post-marketing surveillance
		Limited viral clearance	Specification setting	Stability
		Limited stability	Manufacturing scale up	
			Stability	
			Viral Clearance	

Adapted from a slide by Tony Mire-Sluis

Data Collection During Biosimilar Product Development

Preclinical Toxicology Studies
Short term ⟶

351(k) package

IND Enabling	Initial Clinical Studies	Additional Clinical Studies

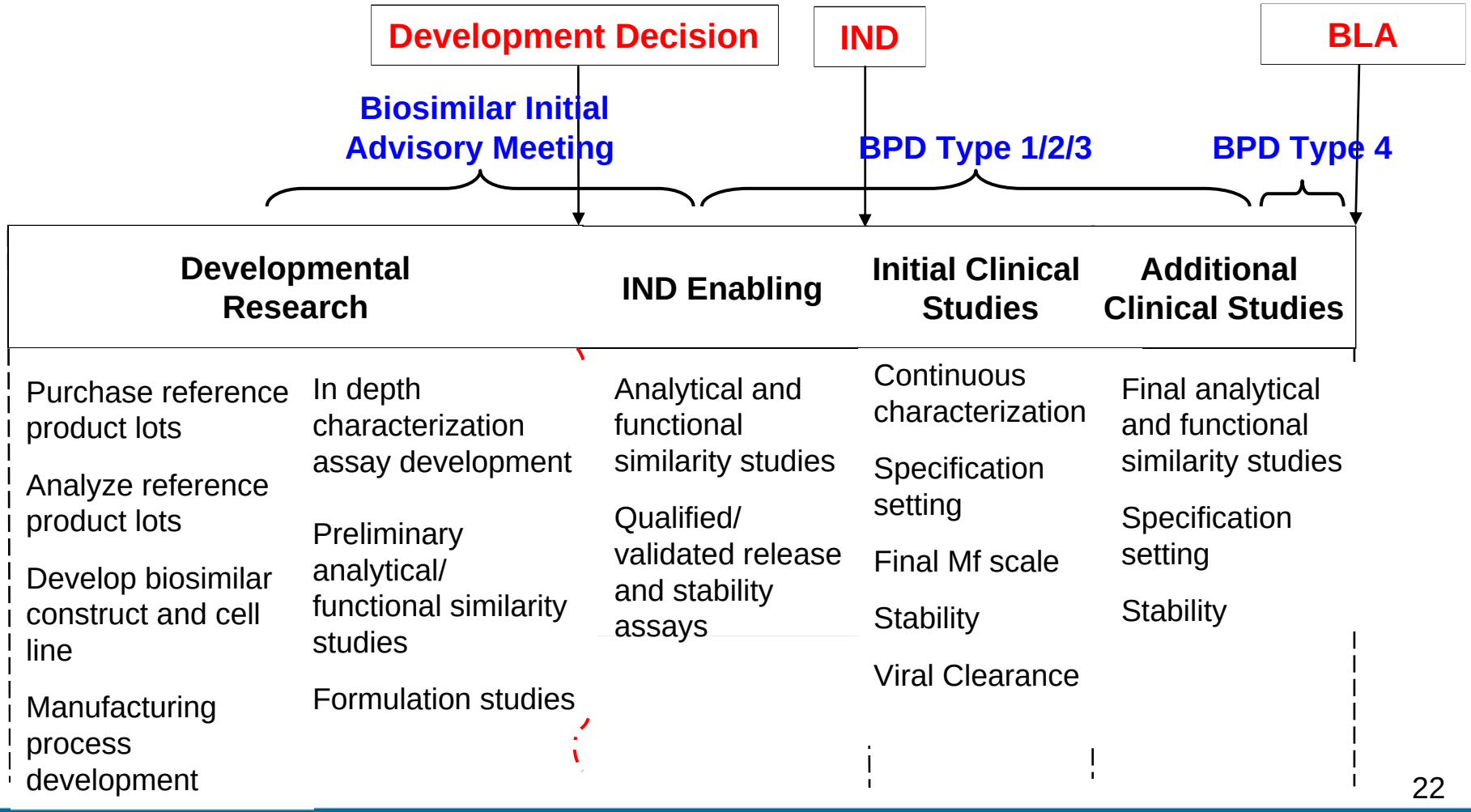
Clinical Studies
PK/PD

Immunogenicity
Additional Clinical Studies

Product Quality

Depends on extent of analytical similarity and PK/PD similarity prior to this point

Preferred Biosimilar Product Quality Development Process



Development Framework:
Comparative Analytical Characterization Continuum

- Cannot be biosimilar
- Similar
  - Needs additional information to determine if highly similar (e.g., additional analytical data, or other studies to determine if minor differences are “clinically inactive components”)
- Highly similar
  - Permits a selective and targeted approach to determine if biosimilar
- Highly similar with fingerprint-like similarity
  - Permits a more selective and targeted approach to determine if biosimilar

Acknowledgements

- Steve Kozlowski
- Leah Christl
- Emily Shacter
- Tony Mire-Sluis

A PhRMA Member View on Biosimilar
Analytical and Quality Considerations

Robert J Mattaliano, Ph.D., Group VP, Biologics Development

Jade (with her mother) Fabry disease USA

FDA Advisory Committee on
Pharmaceutical Science and Clinical Pharmacology
August 8, 2012

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Outline

- Introduction
- Inherent Complexity of Biologics
- Draft FDA Guidance on Biosimilars
- A Few Examples To Consider
- Summary Comments

Genzyme's Mission - to discover and deliver transformative therapies for patients with rare and special unmet medical needs, providing hope where there was none before.

- **Founded in 1981 and pioneered treatments for rare diseases**
- **Serving patients in over 100 countries**
- **Strong relationships with patients and patient communities**
- **Driven by Science**
  - Broad range of technology platforms
  - Closely integrated with clinical, commercial, regulatory, patient advocacy
- **We now benefit from the reach and resources of Sanofi, one of the world's largest pharmaceutical companies**

Campath® Alemtuzumab For Intravenous Use Only

Cerezyme® imiglucerase

Fabrazyme® agalsidase beta

Lumizyme® (alglucosidase alfa)

Myozyme® (alglucosidase alfa)

Thyrogen® (thyrotropin alfa for injection)

Megan Pompe USA

Next-generation therapies for Gaucher, Fabry and Pompe diseases

Research in Niemann-Pick B, Lupus, MS, Parkinson's and Cystic Fibrosis

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Biologics versus Small Molecule Drugs

Biologics

- Larger, complex, dynamic structures
- Diverse populations of molecules not easily characterized
- Produced using a biological process
- Complicated manufacturing
- *Example: Monoclonal antibodies*

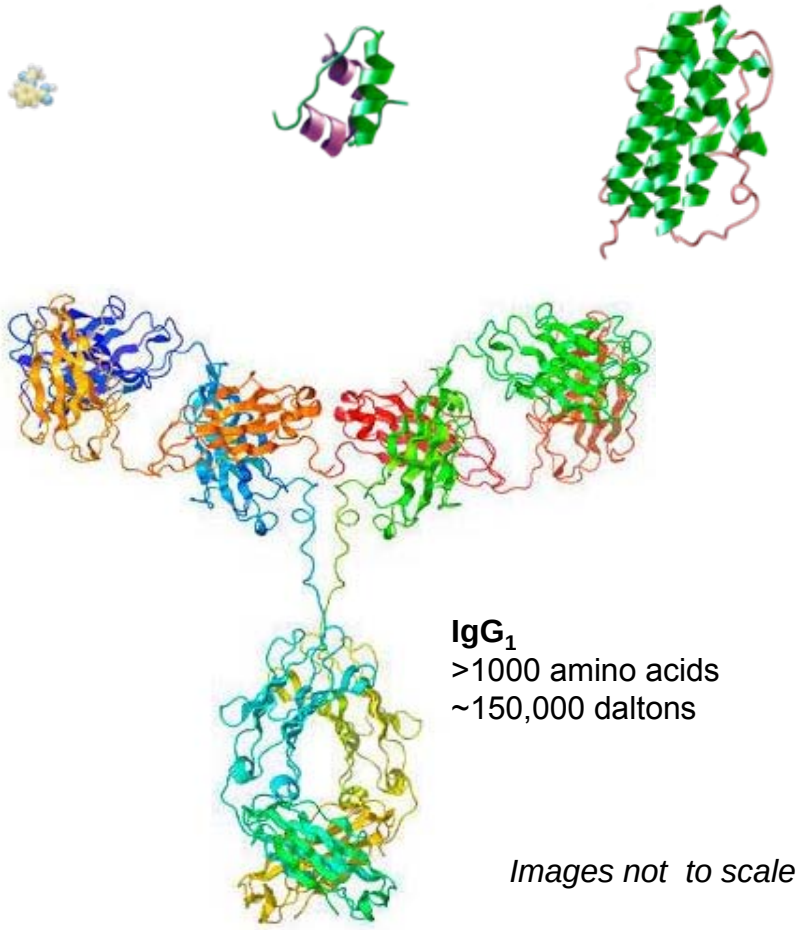
Small Molecule Drugs

- Synthetic
- Manufacturing processes using defined chemical reactions
- Smaller, simpler structures – can be fully characterized by standard analytical techniques
- *Example: Aspirin*

Aspirin
~180 daltons

Insulin
51 amino-acids
~5,800 daltons

Somatropin
191 amino-acids
~22,000 daltons



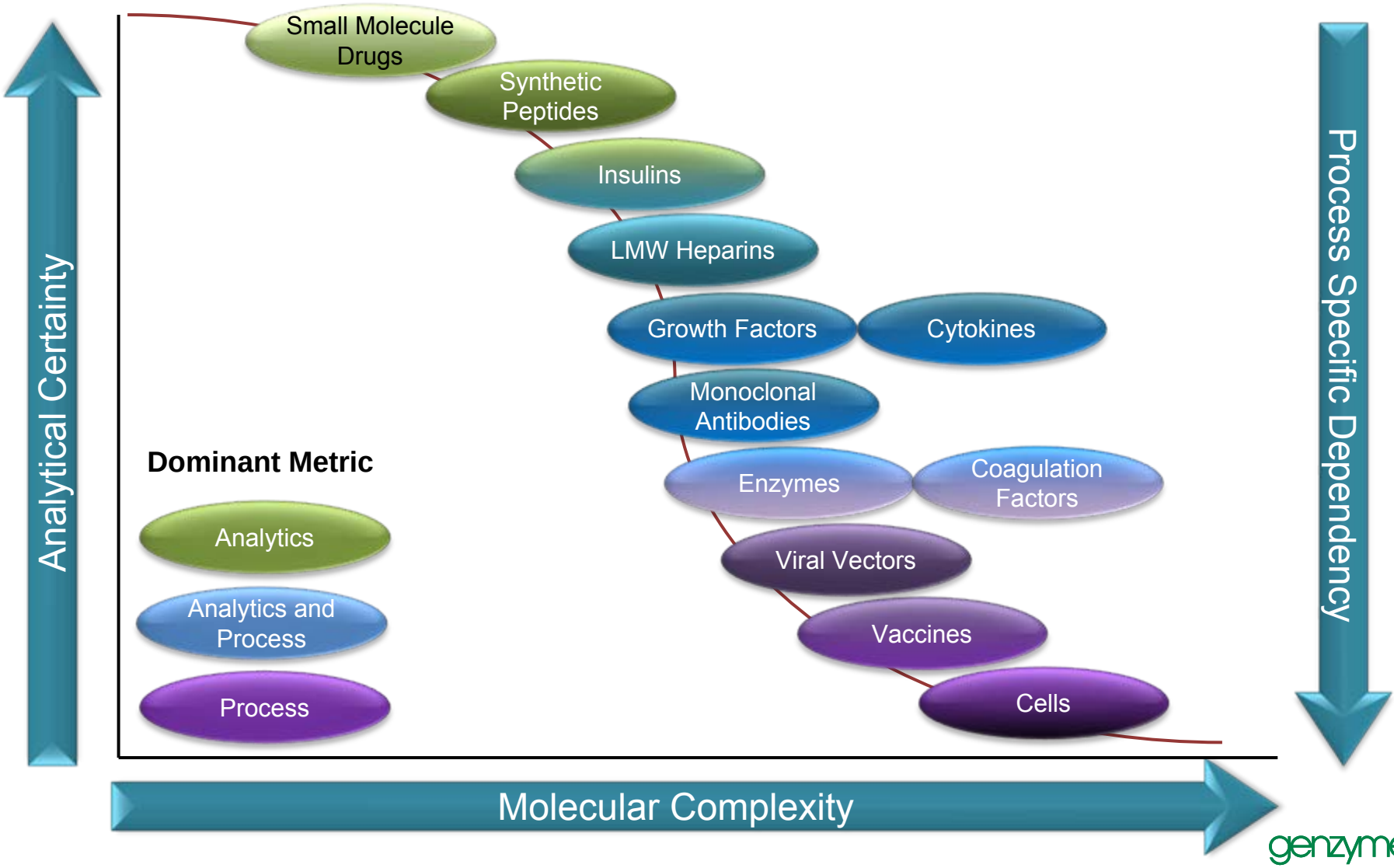
IgG_1
>1000 amino acids
~150,000 daltons

Images not to scale

Data sources: www.jtbaker.com, http://www.umass.edu/microbio/chime/antibody/abquests.htm

Not All Biologics Are Created Equal

Gradations of Complexity



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Probing the Quality and Consistency of Biologics

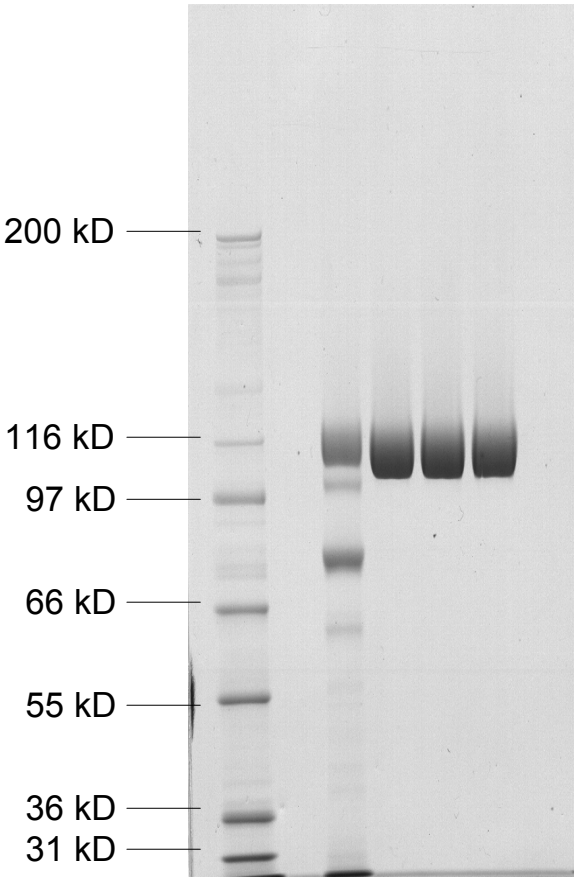
Quantitative and Qualitative Tools - Many Form the Basis for Release Tests

- **Protein Structure**
  - Primary Sequence Confirmation
  - Identity
  - Disulfide Bonding Pattern
  - Secondary, Tertiary and Quaternary Structures
  - Molecular Weight Analyses
  - Glycan Attachment Sites
- **Drug-related Substances and/or Impurities**
  - Electrophoretic Purity (reducing and non-reducing denaturing conditions)
  - Chromatographic Purity (various stationary phases)
  - Soluble Oligomer and Aggregate content
  - Particle Content
- **Process-related Substances and/or Impurities**
  - Host Cell Impurities
  - Host Cell DNA
  - Process related Impurities (e.g., Protein A, metals, solvents)
  - Process Extractables, Leachables
- **Post-Translational Modifications**
  - Individual Monosaccharide Content (e,g., NANA, NGNA, fucose, phosphorylated mannose)
  - Oligosaccharide Profiling, Site Specific Glycoform Analysis
  - Amino Acid Modifications (e.g., deamidation, oxidation)
  - Degree of Proteolytic Fragmentation
- **Function / Potency**
  - Bioassays
  - Receptor Binding
  - Cellular uptake/processing
  - Enzymatic Activity/Kinetics
- **Stability**
  - Biologic and Impurity attributes under proposed storage conditions
  - Thermal-, pH-, Photo-Stability under controlled stress conditions
- **General Methods**
  - Appearance, Concentration, pH, Endotoxin, Sterility
- **Non-Clinical Analyses in Relevant Animal Models**
  - Pharmacokinetics
  - Biodistribution
  - Pharmacodynamics

Apparent Molecular Complexity

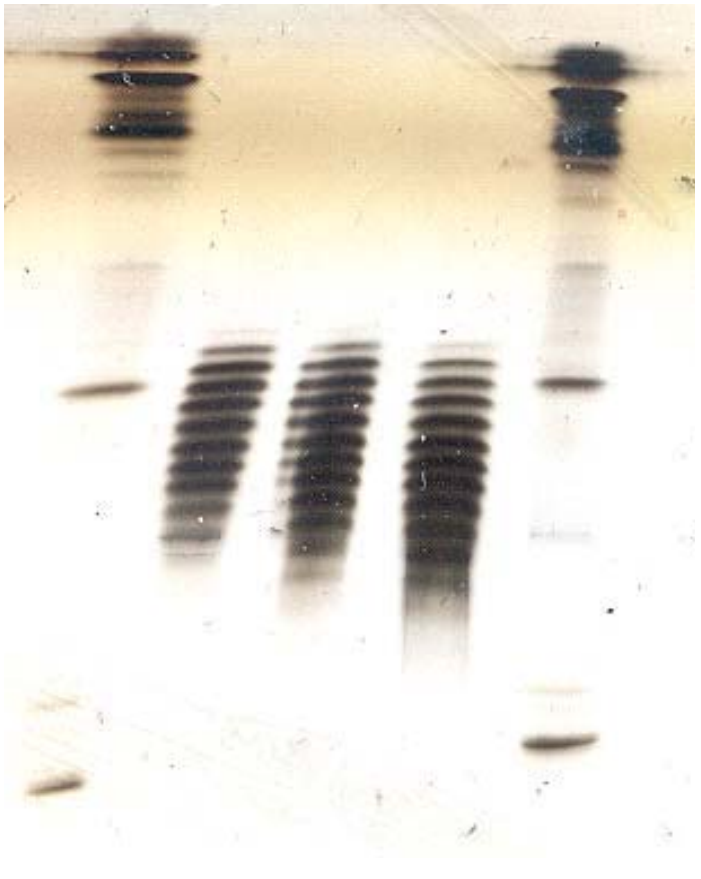
Depends on the Method Being Used

Separation Based Molecular Mass



SDS-PAGE

Separation Based Molecular Charge



Isoelectric Focusing

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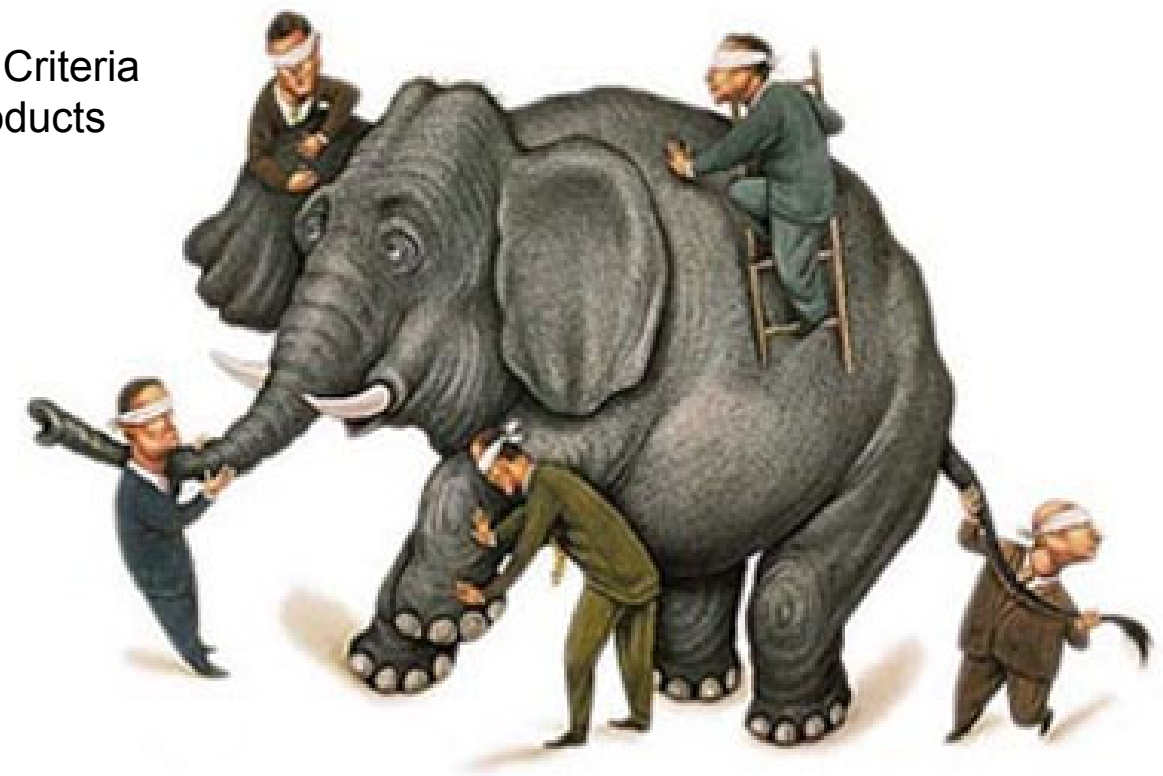
Why Multiple Approaches Are Used?

An Exercise in Pattern Recognition

ICH Topic Q6B
Specifications:
Test Procedures and Acceptance Criteria
for Biotechnological/Biological Products

The manufacturer should define **the pattern of heterogeneity** of the desired product and **demonstrate consistency** with that of the lots used in preclinical and clinical studies.



Protein Post-Translational Modifications
A Quantum Leap to Proteome and Biologics Diversity

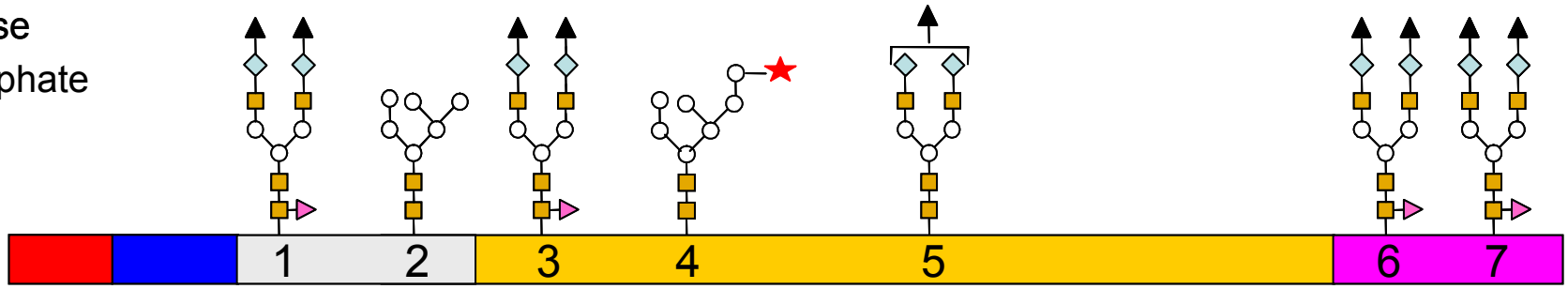
- **Protein amino acids are often covalently modified in the cell to critically confer structure, function and stability**
- **15 of 20 amino acids have known modifications**
  - **10 residues (Arg, Asp, Cys, Glu, His, Lys, Met, Ser, Thr, Tyr) have reactive N, O, or S atoms**
  - **2 residues (Asn, Gln) contain reactive amide containing side chains**
  - **3 residues which are less reactive (Trp, Pro, Gly)**
  - **5 residues (Leu, Ile, Val, Ala, Phe) with no reported modifications**
- **Post-Translational Modifications include**
  - **Disulfide bond formation**
  - **N- Glycosylation, O- Glycosylation**
  - **Deamidation, Asp Isomerization**
  - **Oxidation**
  - **Phosphorylation**
  - **Carboxylation**
  - **-Methylation**
  - **-Poly-glycination, -glutamination**
  - **-C-hydroxylation**
  - **-Transglutamination**
  - **-Sulphation**
  - **-Lipidation**
- **The type and degree of PTM's varies with expression cell type and specific production process**

Post Translational Modifications

Consider Glycosylation

- Sialic Acid
- Galactose
- N-acetyl Glucosamine
- Mannose
- Fucose
- Phosphate

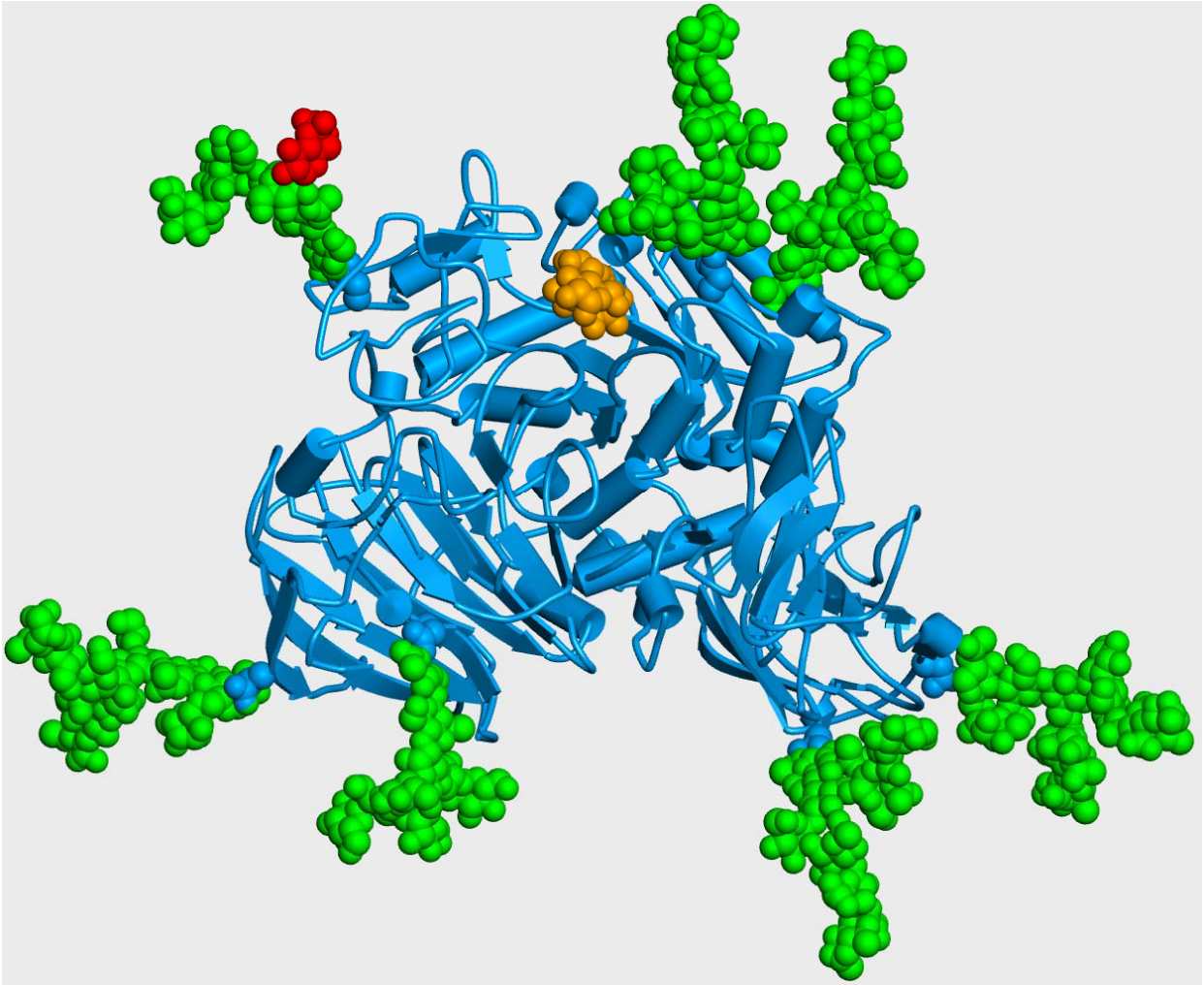
Glycosylation Variants Inform Targeting and Clearance



	1	2	3	4	5	6	7
significant glycan structures / site	10	10	5	11	4	7	10

~ 1.54 x 10^6 possible variants based on predominant site specific glycans alone

Sophisticated Models May Imply a Higher Level of Understanding of Molecular Complexity



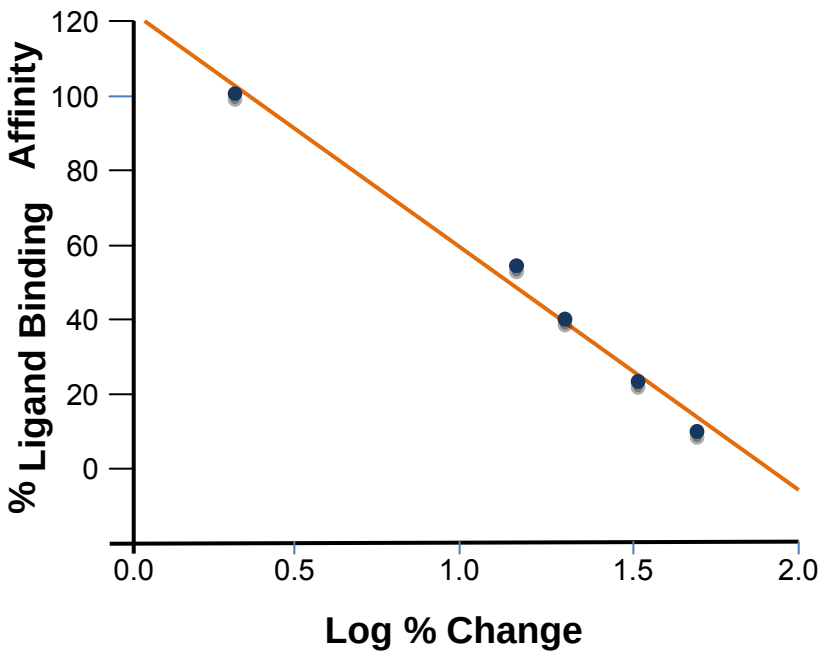
Model of glucosidase acid alpha based on the structure of maltase-glucoamylase complexed to an active site inhibitor (Sim et al, 2008 JBC). Courtesy of R. Wei, C. Pan

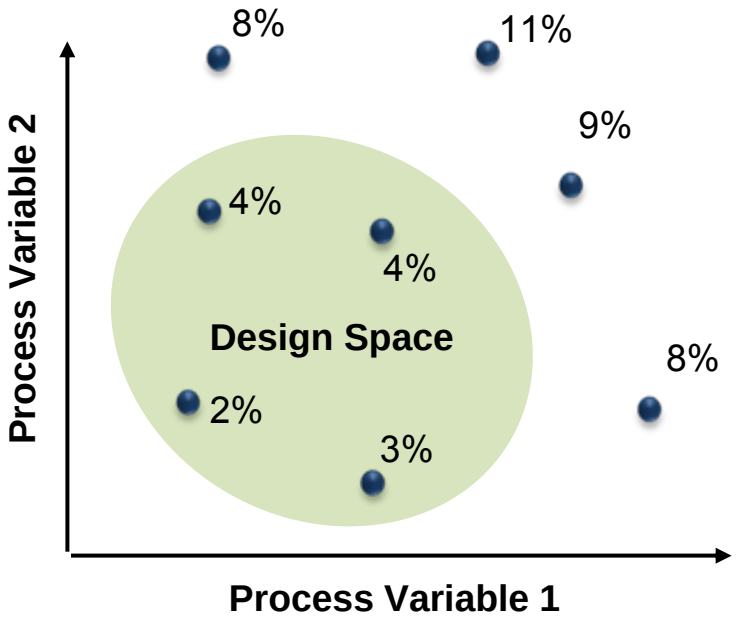
Making Gains on Our Understanding of Diverse Populations of Structurally Complex Molecules

- **Our industry has been greatly enabled by advances in analytical technologies and methods**
  - e.g., Mass Spectrometry, Ultra Performance LC, NMR, Sensitive Biophysical Methods, Capillary-, Chip-Based Methods, Receptor Binding (SPR), Sophisticated Bioassays, Better Animal Models, Imaging Tools, Ultra-sensitive Immunoassays, Robotics, Computer Science, ….
- **Unfortunately, our ability to probe the inherent complexities of many biologics remains imperfect**
- **Seemingly small changes to a biologics structure or population diversity may have unintended clinical consequences**
- **Consequently, the specific production process, controls and clinical experience often define product safety and efficacy**
- **What distinguishes innovators from biosimilar manufacturers are insights regarding critical quality attributes and experience producing a particular product**

Identifying Biologics Critical Attributes is Key

A single amino acid essential for a MAb function





- MAb-ligand crystal structure solved
- Limited engineering alternatives
- Strategy => Adapt the Process Control Strategy
- Refine Process Design Space

On-Going and Emerging Areas of Investigation

- Impact of codon optimization (i.e., codon bias)[1]
- Different types and levels of post-translational modifications (e.g., glycosylation)
- Understanding molecular flexibility / surface dynamics
- Controlling the diversity of complex molecular populations
- Mitigating physical instabilities (e.g., aggregates, particles)
- How trace impurities may facilitate immunogenic responses[2]
- Reactivity of product contact disposables (e.g., extractables, leachables)

[1]Sauna, Kimchi-Sarfaty. Nature Reviews: Genetics. 12, 683-691. Oct 2011
[2]Verthelyi, Wang. PLoS ONE. 5(12) e15252. Dec 2010

Biologics Are Not Monomolecular Entities

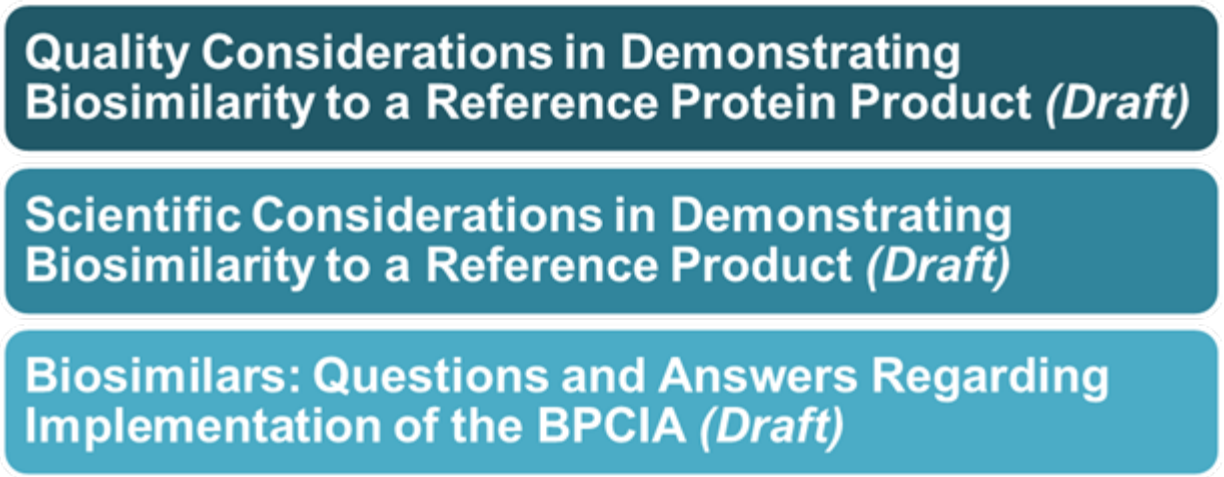
Two Central Questions Arise Regarding Biosimilars

To what extent can innovator product sampling provide a sufficient picture of reference biologic complexity and manufacturing history to assess biosimilarity?

Can comparative analytical testing assure no meaningful differences from a reference biologic clinical safety, purity, and potency?

FDA Draft Guidance to Industry Relating to Implementation of BPCIA 2009

- In February 2012, FDA issued three draft guidance documents on biosimilar product development to assist industry in developing these products



- When finalized, these guidances will represent the FDA's current thinking on these topics

Recognizing One's Limitations

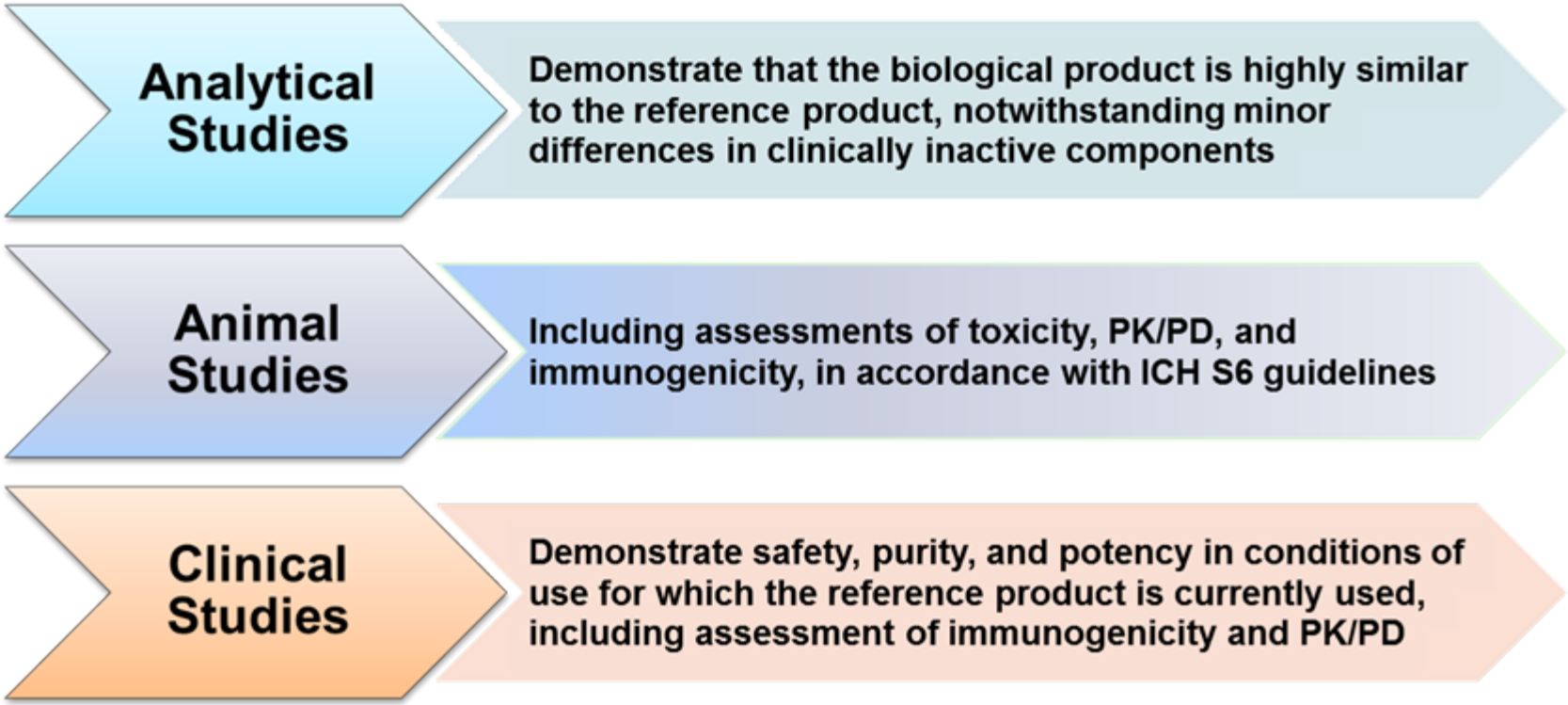
The Definition*

"the biological product is **highly similar** to the reference product, notwithstanding minor differences in clinically inactive component", **and** "there are **no clinically meaningful differences** between the biological product and the reference product in terms of the safety, purity, and potency of the product".

Recognizing an analytical program's limitations is equally important as, if not more important than, recognizing its strengths.

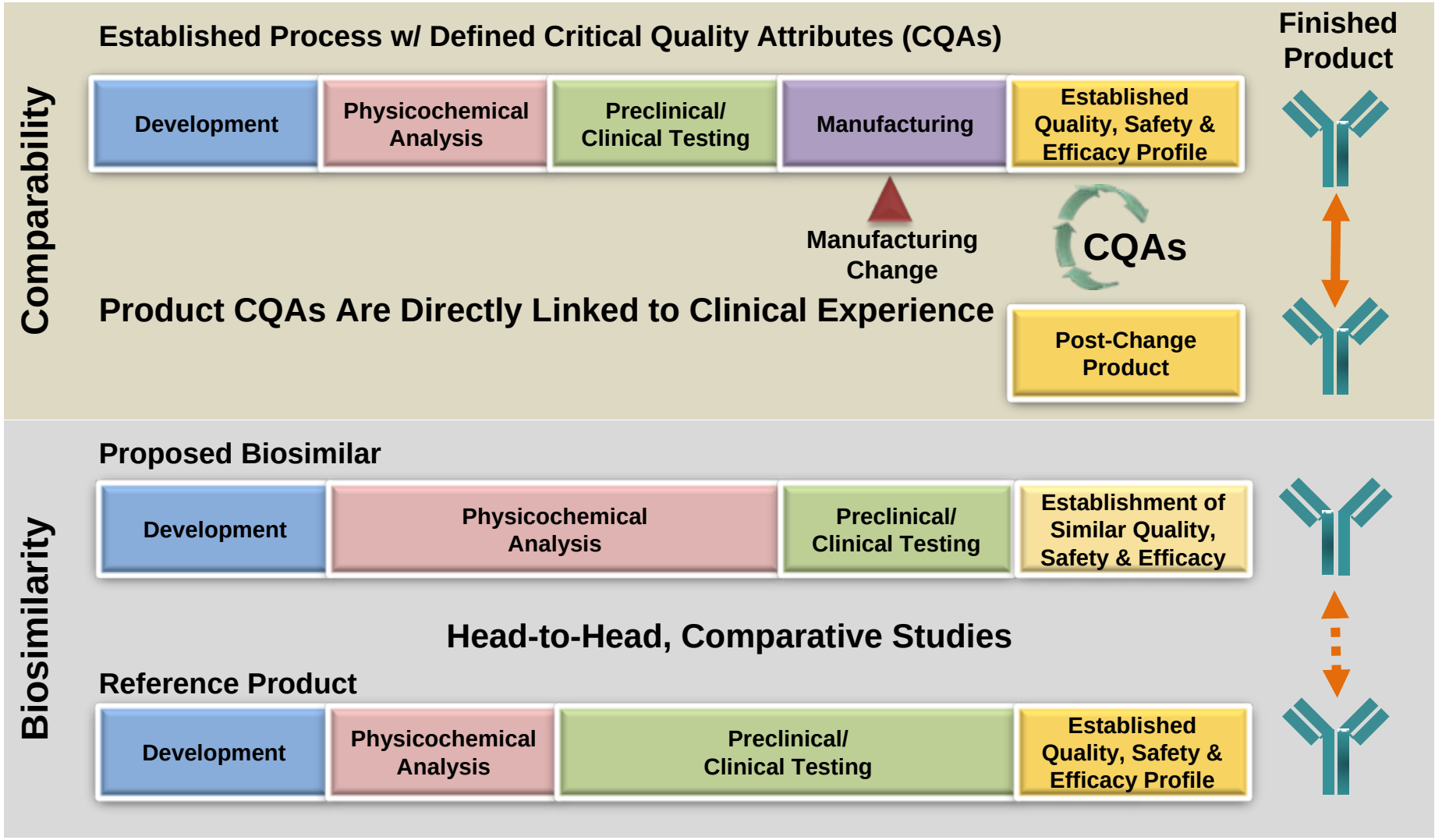
*Scientific Considerations in Demonstrating Biosimilarity to a Reference Product (FDA Draft Guidance, February 2012)

FDA's Stepwise Approach to Demonstrate Biosimilarity
Assuring Patient Safety is Paramount

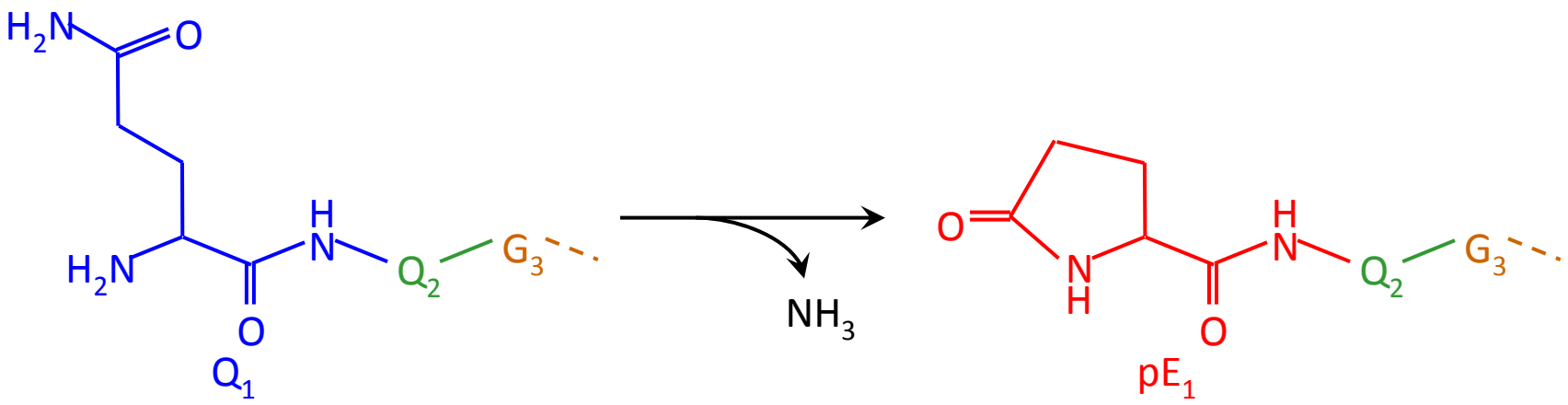


- FDA proposes to use risk-based, totality-of-the-evidence approach to evaluate all available data and information
- However, FDA has the discretion to determine that an element above is *unnecessary* for approval

How Will Biosimilar Sponsors Identify Critical Quality Attributes?



Sorting Out Which Attributes Are Critical
Example - N-terminal Heterogeneity/Cyclization

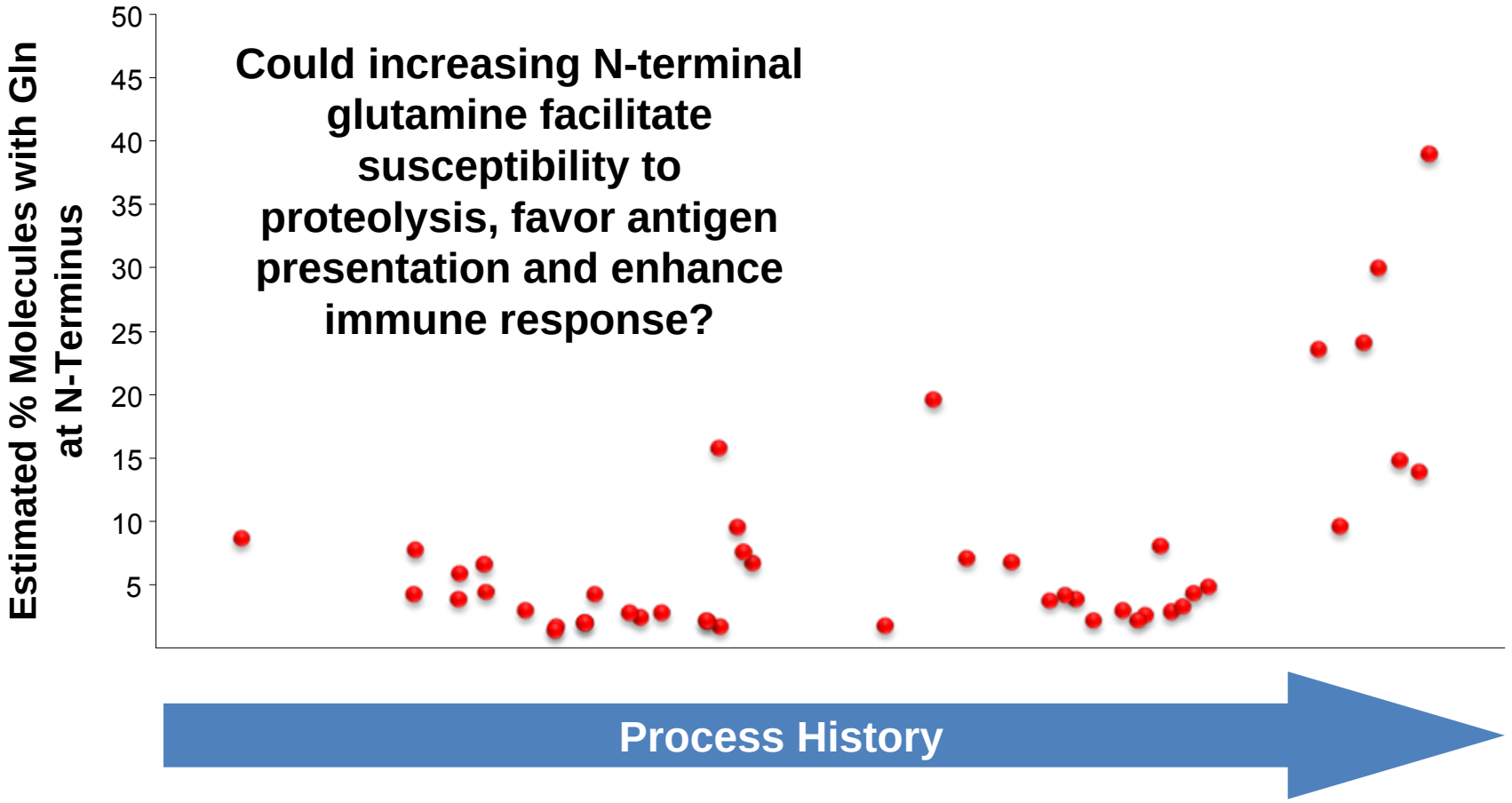


N-terminal glutamine (Q) **Pyroglutamic acid**

- Common post-translational modification (e.g., MAb H, L chains)
- Thermodynamically favored
- Catalyzed by glutaminyl cyclase (many plants and animals, including humans)

Cyclization of N-Terminal Glutamine to Pyroglutamic Acid

May Be Directly Impacted by Manufacturing Process Intermediate Hold Times

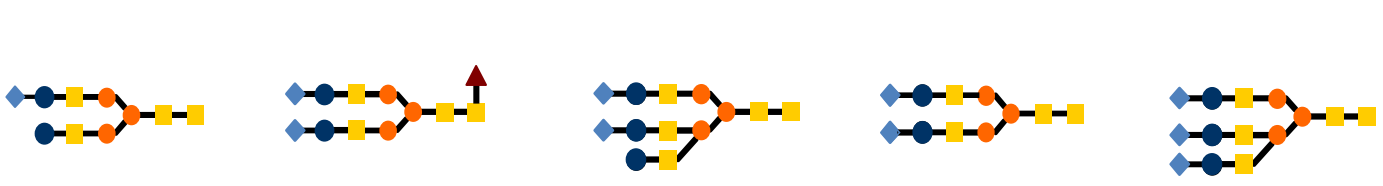


Experimental Confirmation is Key
Example - N-terminal Heterogeneity/Cyclization

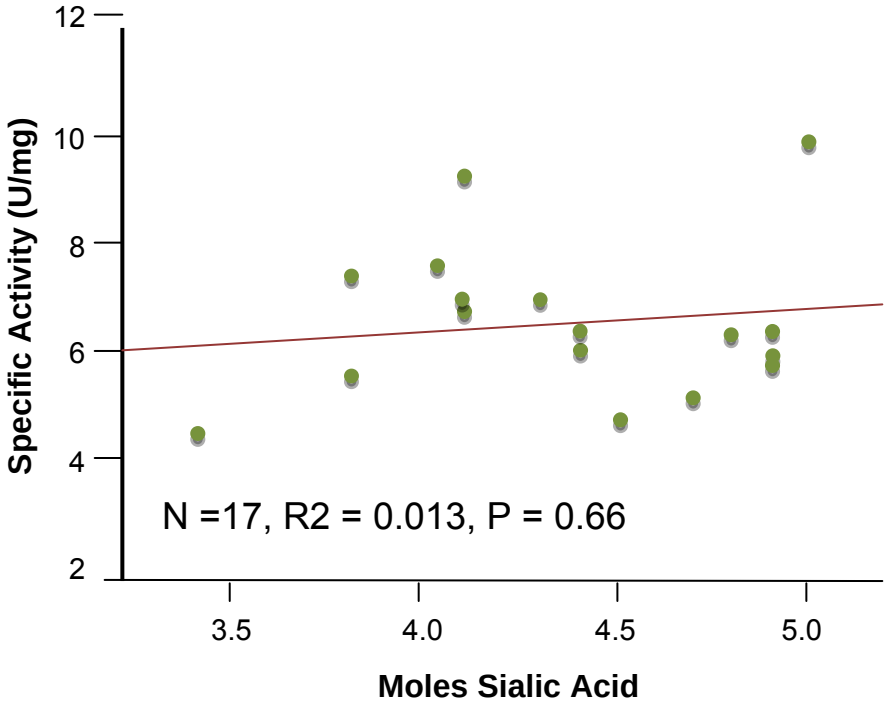
- Removal of N-terminal pyroglutamic acid had no measurable effects on higher order structure , activity, ligand binding, cellular uptake, aggregation, degradation, pharmacodynamics or biodistribution
- Hypothetical concerns of N-terminal heterogeneity on immunogenicity
  - Conflicting literature with respect to relative immunogenicity for N-terminal glutamine vs. pyroglutamic acid using peptide models
- Sera from patient with neutralizing or high titers did not cross react with N-terminal epitopes of the biologic; thus, no apparent role for N-terminus in immunogenicity

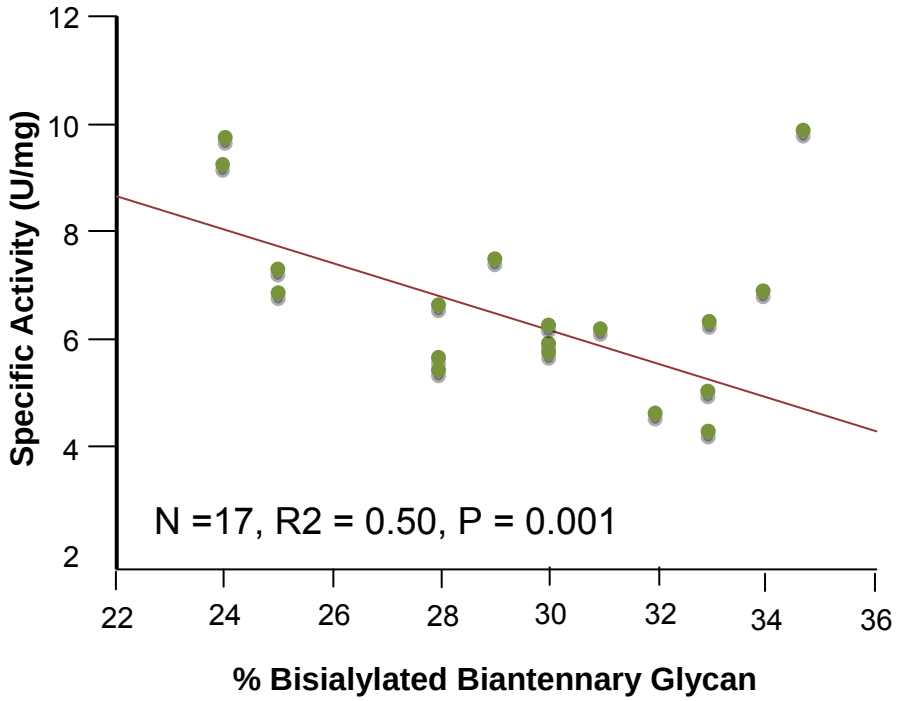
Identifying Critical Attributes

Example – Sialylation Positional Differences on Complex Glycans



GlcNAc
Mannose
Galactose
Fucose
NANA





genzyme
A SANOFI COMPANY

Even When Biologics Are “Highly Similar”
Expect the Unexpected

Critical Quality Attribute*			
Process	A	B	Pharmacokinetic Equivalence
1	165	67	No
2	91	81	

* Percentage of Reference Value

Even When Biologics Are “Highly Similar”
Expect the Unexpected

Critical Quality Attribute*			
Process	A	B	Pharmacokinetic Equivalence
1	165	67	No
2	91	81	
1	115	119	Yes
2	115	67	

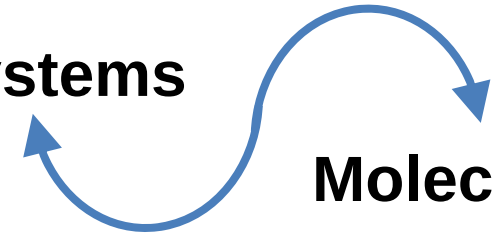
* Percentage of Reference Value

Even When Biologics Are "Highly Similar"
Expect the Unexpected

Critical Quality Attribute*			
Process	A	B	Pharmacokinetic Equivalence
1	165	67	No
2	91	81	
1	115	119	Yes
2	115	67	
1	171	86	No
2	159	86	

* Percentage of Reference Value

Considering The Implications of Change
(e.g., Biologics Source, Process, Clinical Indication)



How well do we understand the disease, indication?	Etiology and pathology, associated structural and functional defects
How well do we understand the drug, critical quality attributes and production process?	Identity, purity, potency, ADME, safety, manufacturability, specificity
How well do we understand the mechanism of action with respect to the disease/indication we are targeting?	Strength of target validation in the context of the clinical disease
How well can we follow the effect of our drug on the disease/ indication we are targeting?	Biomarkers, imaging, type of specimens

PhRMA's Overarching Principles on Regulatory Pathways for Biosimilars

- **Patient safety should be <u>paramount</u> when evaluating proposed biosimilar products**
- The statutory standard for biosimilarity rests in the negative — in establishing the absence of clinically meaningful differences
  - An abbreviated licensure pathway is appropriate only when a biological product has been demonstrated to be highly similar to, and devoid of any clinically meaningful differences from, a single FDA-approved reference product
- A clear, scientifically rigorous process for evaluation of potential differences between a proposed biosimilar and its reference product is essential to ensure, <u>for patients,</u> the quality, safety, and efficacy of the biosimilar

PhRMA

Some Concluding Thoughts

- We should be humble about what we don't know
- Being wrong may have serious consequences for drug efficacy and patient safety

- We are making progress linking some, but not all, biologics properties to critical quality attributes
- The lenses and model approaches through which we examine biologics have room for improvement
- Innovators have detailed information on numerous drug product lots which can be directly linked to clinical experience

- Given the gradation of biologics complexity, a one size fits all strategy for biosimilars will not be possible

FDA ACPS-CP UPDATE ON BIOSIMILARS

On Behalf of GPhA

Mark McCamish, MD, PhD

Global Head Biopharmaceutical Development

Sandoz International

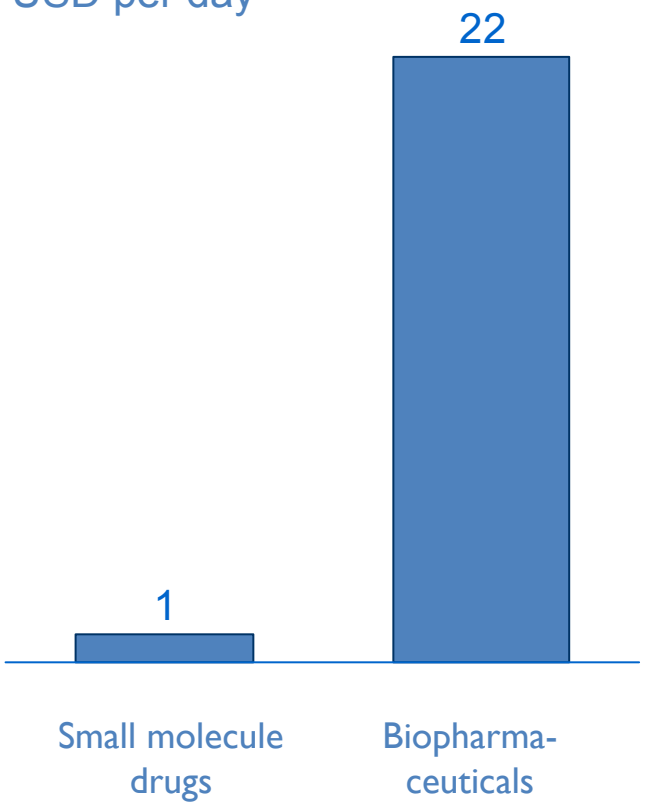
FDA White Oaks Conference Center, Silver Spring, MD, 8 August 2012

OVERVIEW

- Why biosimilars?
- Scientific approach to biosimilar development
- Abbreviated clinical trial designs
- Successful commercialization broadens patient access

GROWING DEMAND DRIVES COSTS… AND THREATENS TO LIMIT PATIENT ACCESS

Estimated daily treatment costs[1]
in USD per day



The "Biologics Boondoggle"

"A breast cancer patient's annual cost for Herceptin is $37,000…

People with rheumatoid arthritis or Crohn's disease spend $50,000 a year on Humira…

…and those who take Cerezyme to treat Gaucher disease….spend a staggering $200,000 a year…

"…the top six biologics already consume 43% of the drug budget for Medicare Part B"

The New York Times
Expect the World®

[1] **Source: NY Times, March 2010**

BY 2016, 7 OF THE TOP 10 PHARMACEUTICALS WORLDWIDE WILL BE BIOLOGICS[1]

Product	Type	2016 Rev. (USD bn)	2010 Rev. (USD bn)
1. HUMIRA	Biologic	10.0	6.7
2. AVASTIN	Biologic	7.7	6.2
3. RITUXAN	Biologic	7.6	6.1
4. ENBREL	Biologic	7.1	7.3
5. CRESTOR	Small molecule	7.5	6.0
6. SERETIDE/ADVAIR	Respiratory / device	6.7	7.9
7. REMICADE	Biologic	6.2	6.5
8. HERCEPTIN	Biologic	6.3	5.2
9. REVLIMID	Small molecule	6.1	2.5
10. LANTUS	Biologic	5.3	4.7

[1] **Source: Evaluate Pharma, Sandoz analysis**

OVERVIEW

- Why biosimilars?
- **Scientific approach to biosimilar development**
- Abbreviated clinical trial designs
- Successful commercialization broadens patient access

FINGERPRINTING AND ENOXAPARIN

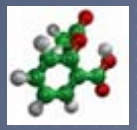
- FDA developed 5 criteria for fingerprinting evaluation of enoxaparin
  - Equivalence of physiochemical properties
  - Equivalence of heparin source material and mode of depolymerization
  - Equivalence in diasaccharide building blocks, fragment mapping and sequence of oligosaccharide species
  - Equivalence in biological and biochemical assays
  - Equivalence of in vivo pharmacodynamic profile

FDA: "The five criteria ensure that generic enoxaparin will have the same active ingredient components as those of Lovenox's enoxaparin (within the context of its variability) even though the contribution of each component has not been fully elucidated. Therefore, pharmacological activity of the active ingredient of the generic enoxaparin and that of Lovenox can be expected to be the same."

For good review see: BioCentury, Vol 18, Aug 2010, "Equivalence test case, by Susan Shaeffer

BIOLOGICS ARE MORE COMPLEX THAN SMALL MOLECULES AND MABS MORE COMPLEX THAN SIMPLE BIOLOGICS

Aspirin®



small chemical molecule

Molecular weight
= 180 Daltons
0 amino acids

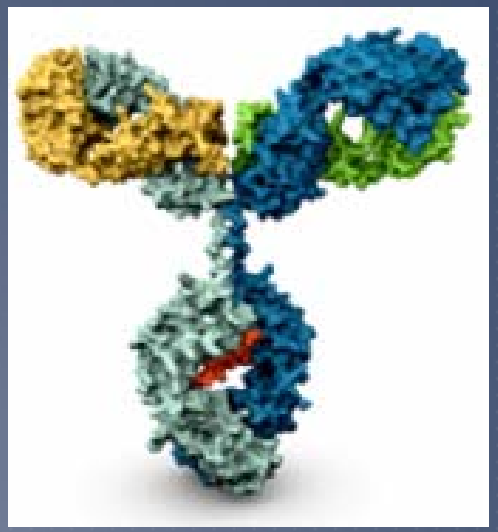
Calcitonin

simple biologic

Molecular weight
= 3,455 Daltons
~ 32 amino acids

- w/o host cell modifications
- produced in yeast, bacteria

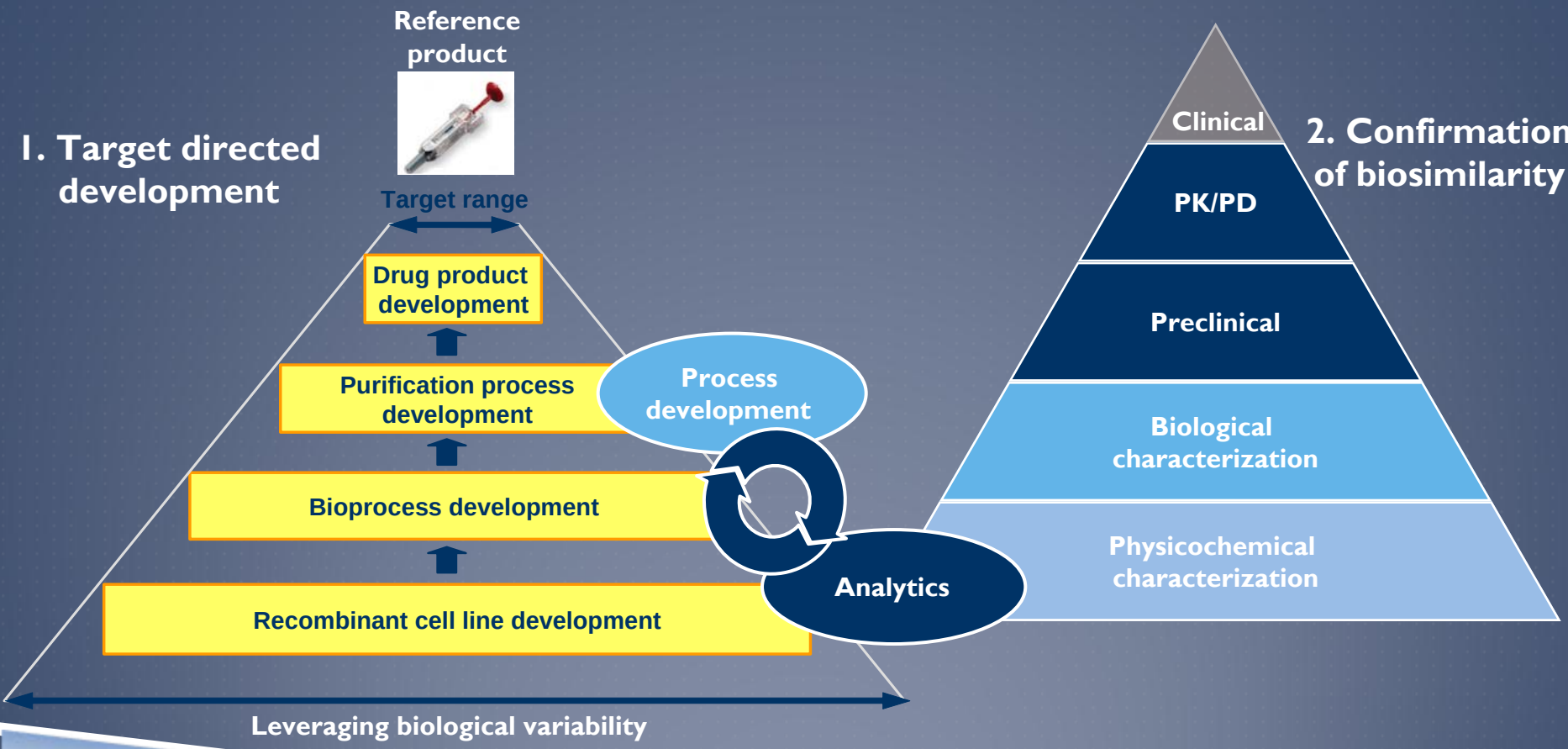
Monoclonal Antibody (IgG)



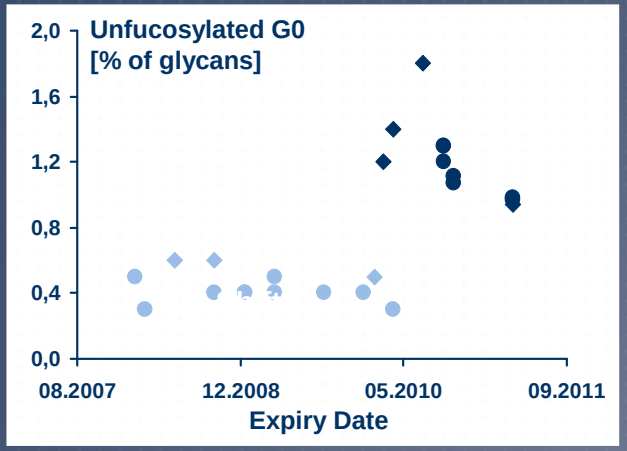
complex biologic

Molecular weight
= 150,000 Daltons
~ 1300 amino acids
- w/host cell modifications
(glycosolations, etc)
- produced in mammalian cells

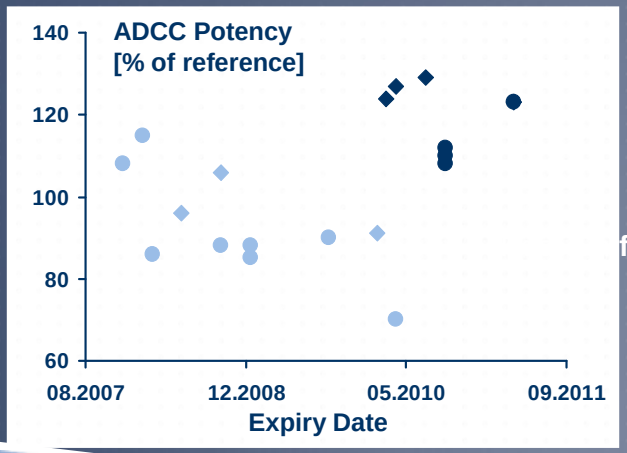
BIOSIMILARS MUST BE SYSTEMATICALLY ENGINEERED TO MATCH THE REFERENCE PRODUCT



"ACCEPTABLE CHANGES IN QUALITY ATTRIBUTES OF GLYCOSYLATED BIOPHARMACEUTICALS"



Post-Shift



Pre-Shift

CORRESPONDENCE

Acceptable changes in quality attributes of glycosylated biopharmaceuticals

To the Editor:

Since the first marketing approvals of recombinant biopharmaceuticals, the question of which changes in quality attributes, which comprise identity, strength and purity are acceptable in the life cycle of these products without changing the product label has been debated extensively[1]. This question is especially important in the context of manufacturing process changes, which happen quite frequently and for various reasons (e.g., process improvements, scale changes or site transfers). Although companies and health authorities have been managing these quality changes for many years based on the principle that changes in quality attributes can be accepted only if they do not alter safety and efficacy, the lack of peer-reviewed data in the public domain has limited debates about product quality and variation to a discussion of principles rather than specifics. Here, we present a study that looks at variation in three major marketed biologics, the purpose of which is to provide more transparency and to anchor the debate about acceptable changes in quality attributes on a firmer factual footing. Identifying such variations in quality attributes could help not only biotech companies in their development efforts but also the medical and scientific communities in understanding these products. By analyzing the quality profiles of the glycosylated recombinant therapeutic proteins Aranesp (darbepoetin alfa), Rituxan/MabThera (rituximab) and Enbrel (etanercept) sourced from the market between 2007 and 2010, our data thus provide examples of acceptable variations for products that have remained on the market with unchanged product labels.

Glycosylated proteins are complex molecules and even a well-controlled product may consist of several hundred or more glycoforms having the same amino acid sequence but different glycan composition. When making these products, the manufacturer has to deliver a consistent product quality to guarantee a reproducible clinical performance. Current analytical methods allow the detection of even small changes in quality attributes and can therefore enable sensitive monitoring of the batch-to-batch consistency and variability of the manufacturing process. Several different factors may account for changes in quality attributes. The first is the inherent batch-to-batch variability in the manufacturing process. Second, process drifts can lead to gradual changes of attributes. Such drifting events are not desired and normally trigger further investigations and corrective actions, or even redevelopment activities to ensure process consistency. Finally, larger and abrupt changes in quality attributes can occur after implementation of manufacturing process changes, which are all too common in the pharmaceutical industry. Although manufacturers try to prevent associated changes in quality attributes, such changes cannot be avoided in every case.

Changes in the biologics manufacturing process are tightly regulated by the health authorities. Manufacturers need to demonstrate that the process change does not alter the clinical safety or efficacy of the biologic product. The evaluation of such changes follows a comparability exercise between the pre- and post-change product, which is focused on the quality level and sometimes, depending on the magnitude of the change and the existing product understanding, also requires comparative data on the preclinical and clinical levels. The principles of the comparability exercise are regulated in guidelines, such as the International Conference on Harmonisation (ICH) Q5E (http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q5E/Step4/Q5E_Guideline.pdf), which acknowledges that "the demonstration of comparability does not necessarily mean that the quality attributes of the pre-change and post-change product are identical, but that they are highly similar and that the existing knowledge is sufficiently predictive to ensure that any differences in quality attributes have no adverse impact upon safety or efficacy of the drug product."

Comparability decisions are difficult to make and require the complete assessment of the existing process and product including the knowledge of structure-function relationships. Others[2] have already acknowledged that a collection of data would be extremely valuable to come to a more informed design and improved assessment of comparability studies. And yet, very little data on commercialized products can be found in the public domain. In an attempt to at least partially fill this gap, we have analyzed multiple batches of Aranesp, Rituxan/MabThera and Enbrel to study the variability in the quality attributes of modern therapeutic proteins currently on the market. The data were generated as described in the **Supplementary Methods**, using the materials listed in **Supplementary Tables 1** and **2**.

The active pharmaceutical ingredient of Aranesp, darbepoetin alfa, is an erythropoiesis-stimulating protein. It represents an engineered analog of human erythropoietin. It differs from endogenous erythropoietin mainly by an alteration of the amino acid sequence that introduces two additional *N*-glycosylation sites, which results in an elongated half-life *in vivo*. The biological activity and clinical effect of erythropoietins is influenced by the glycosylation profile, which needs to be tightly controlled during production[3].

We have characterized commercial batches sourced in the European Union (EU) by capillary zone electrophoresis, which separates isoforms with different charges resulting from varying numbers of sialic acids per molecule (**Fig. 1** and **Supplementary Fig. 1**). The *in vivo* biological activity is known to be dependent on the number of sialic acid units per molecule, which is a result of the available sialylation sites, the extensivity of the *N*-glycans and the completeness of sialylation[3].

The expiry dates of the tested batches span a range from November 2008 to April 2011. We found a change of the isoform

Schiestl, M. *et al.*, *Nature Biotechnology* **29**, 310 312, 2011)

- Monitoring batches of an approved mAb revealed a shift in quality
- Shift in glycosylation (structure) pattern results in different potency in cell-based assays (function)
- Indication of a change in the manufacturing process
- Sandoz observed such shifts in several original products

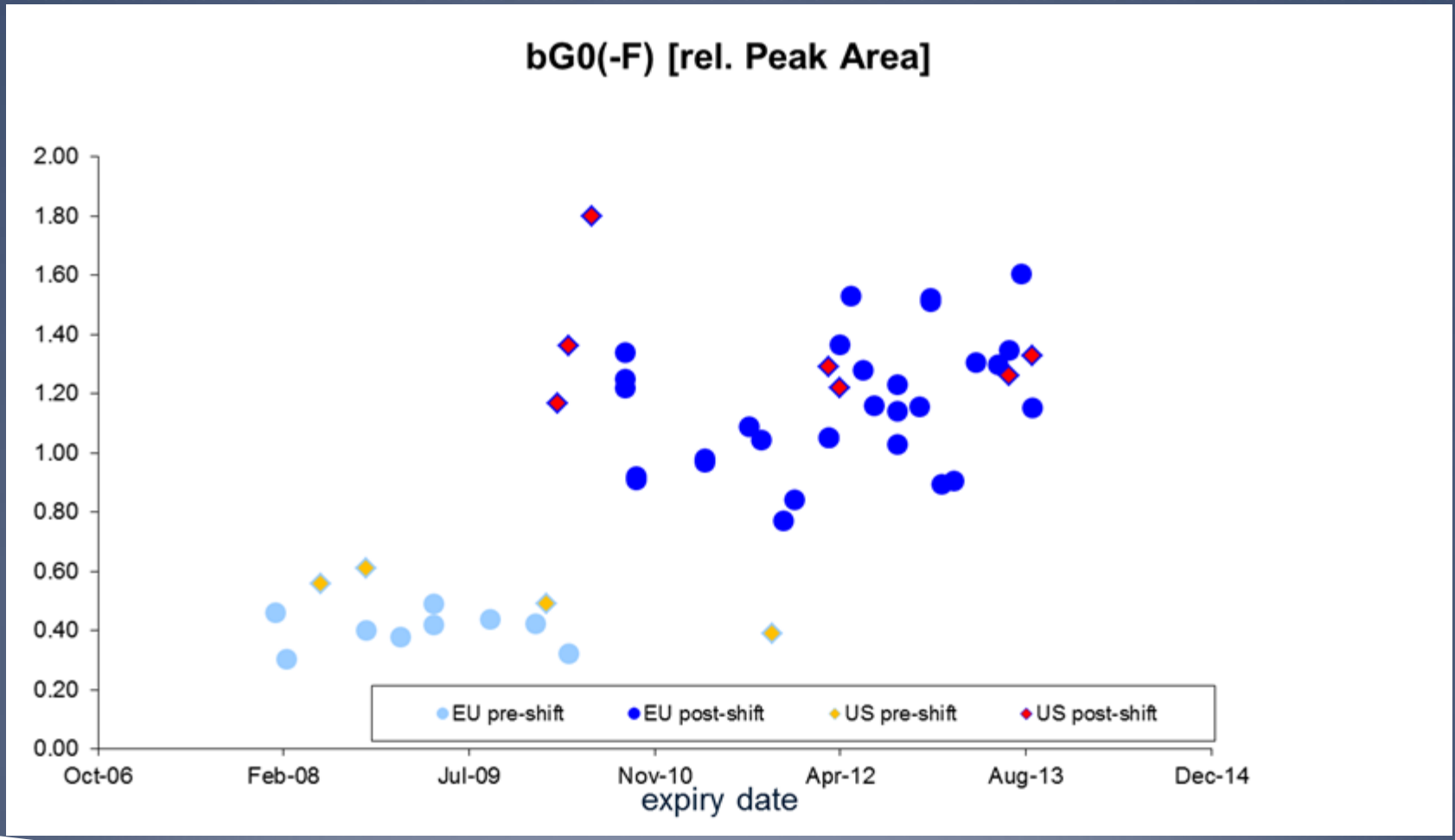
Difference to post-change version sometimes greater than to biosimilar

EMA'S BMWP[1] CONTINUES TO EMPHASIZE THE REGULATORY BASIS OF THE APPROVAL OF BIOSIMILARS

- Biosimilars are intended to be used at the same dose(s) and dosing regimen(s) as the reference product
- Focus is on the **demonstration of (bio)similarity** not patient benefit *per se*
- Extensive comparability exercise to ensure similar quality, safety and efficacy
- Scientific principles underlying the comparability exercise required for changes in the manufacturing process of a given biological product and the development of a biosimilar are the same
- Similar physicochemical characteristics prerequisite for reduction in non-clinical and clinical data requirements

[1]**Martina Weise, MD, BfArM, April 2012 @ EGA International Symposium on Biosimilars**

SIMULTANEOUS QUALITY SHIFTS IN EU AND US REFERENCE PRODUCTS

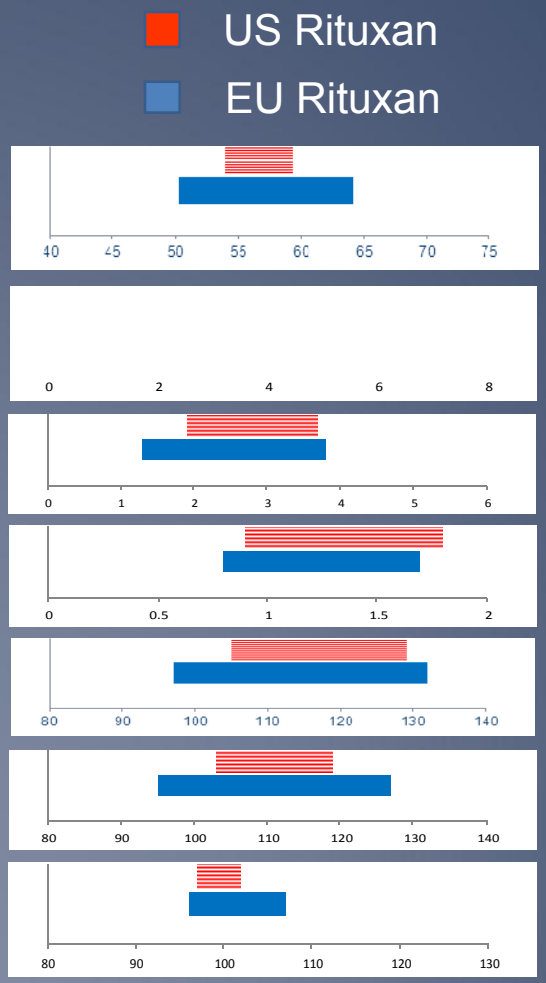


POST-SHIFT EU AND US REFERENCE ANALYTICALLY INDISTINGUISHABLE

	Quality Attribute	Post-shift Rituxan range	Post-shift MabThera range
Charge	**0K**	68.5 – 74.5 (N=5)	67.0 -74.7 (N=14)
	APs	19.8 -24.5 (N=5)	18.8 – 22.0 (N=14)
	BPs	6.3 – 10.4 (N=5)	5.8 – 11.0 (N=14)
	IQ	2.1 – 4.0 (N=5)	1.3 – 4.4 (N=14)
Purity	**SEC**	98.7 – 99.0 (N=12)	98.1 – 99.1 (N=38)
	Aggr.	0.9 – 1.1 (N=12)	0.8 – 1.8 (N=38)

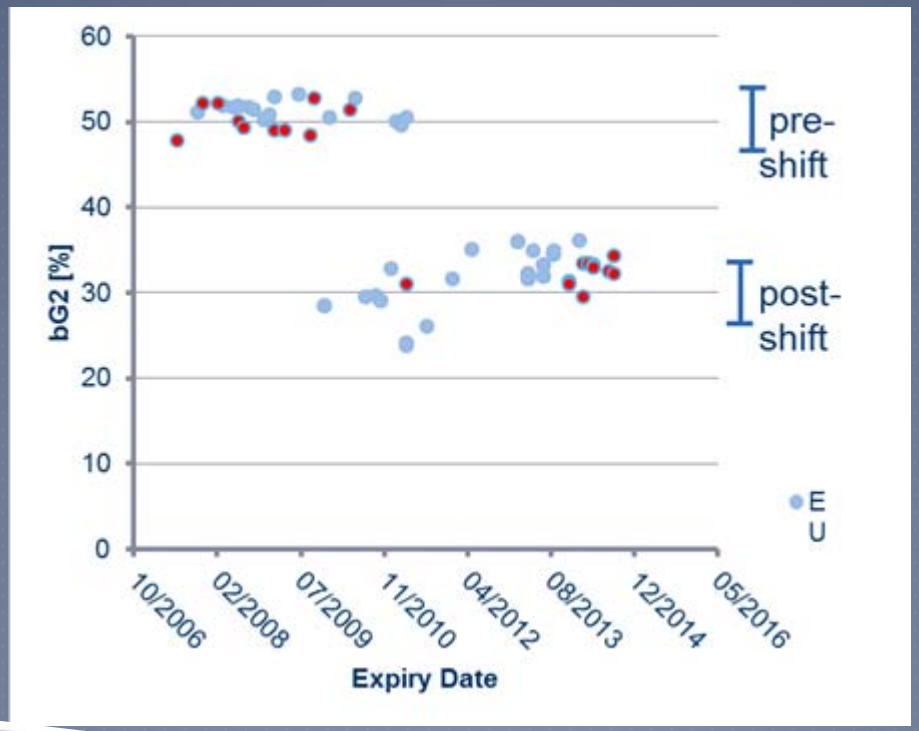
POST-SHIFT EU AND US REFERENCE ANALYTICALLY INDISTINGUISHABLE

	Quality Attribute	Post-shift Rituxan Range	Post-shift MabThera Range
Glycosylation	**Galactosylation**	53.9 – 59.3 (N=8)	50.3 – 64.1 (N=33)
	Sialylation	0.6-3.1 (N=8)	0.5-3.9 (N=33)
	Mannosylation	1.9 – 3.7 (N=8)	1.3 -3.8 (N=33)
	bG0-F	0.9 - 1.8 (N=8)	0.8 – 1.7 (N=33)
Potency	**ADCC**	105 – 129 (N=8)	97 – 132 (N=28)
	CDC	103 – 119 (N=7)	95 – 127 (N=27)
	Binding	97 – 102 (N=3)	96 – 107 (N=22)



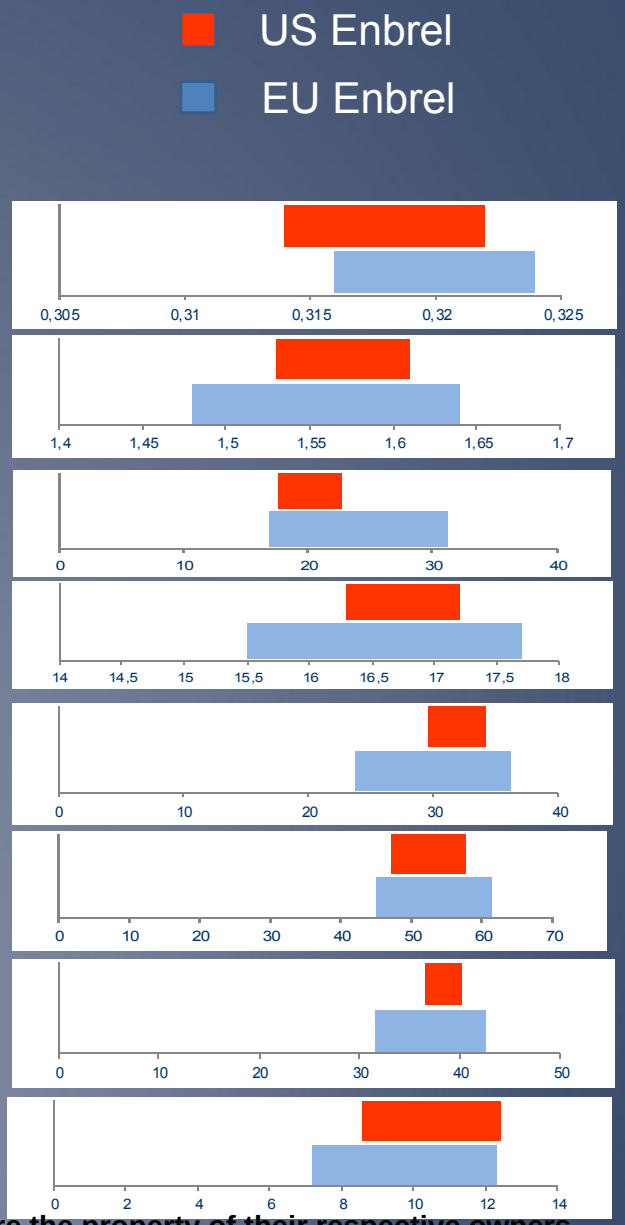
POST-SHIFT EU AND US REFERENCE ANALYTICALLY INDISTINGUISHABLE

- Sandoz started to analyze Enbrel ® US and EU in 2007
- A parallel quality shift in Enbrel was observed in both regions
- The quality shift is independent of the pharmaceutical form



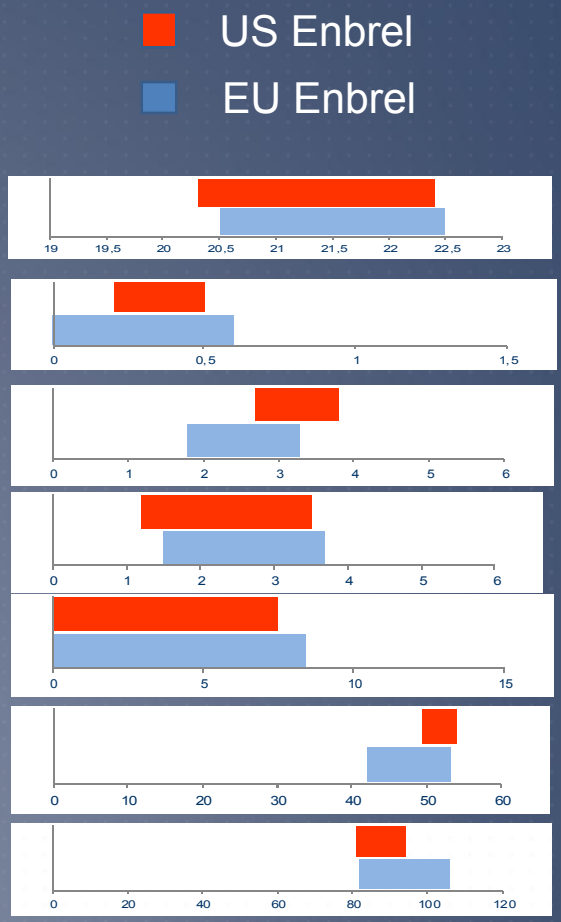
EU AND US ENBREL ANALYTICALLY INDISTINGUISHABLE (PARAMETERS INDEPENDENT FROM PRODUCT AGE)

Attribute	Quality Attribute	Enbrel DP Post-shift range	Enbrel DP Post-shift range
Osmolality	**Osmolality [osmol/kg]**	0.314-0.322 (N=10)	0.316-0.324 (N=11)
Charge	**Overall sialylation (AEX)**	1.53 – 1.61 (N=11)	1.48 – 1.64 (N=17)
Glycosylation	**bG0 [%]**	17.6 - 22-7 (N=13)	16.9 - 31.3 (N=19)
	bG1 [%]	16.3 - 17.2 (N=13)	15.5 - 17.7 (N=19)
	bG2 [%]	29.5 – 34.2 (N=13)	23.7 – 36.1 (N=19)
Sialylation N-glycans	**0S [%] non-sialylated**	47.2 - 57.7 (N=8)	44.9 - 61.2 (N=15)
	1S [%] mono-sialylated	36.6 - 40.2 (N=8)	31.6 - 42.7 (N=15)
	2S [%] di-sialylated	8.6 - 12.4 (N=8)	7.2 - 12.3 (N=15)



EU AND US ENBREL ANALYTICALLY INDISTINGUISHABLE (PARAMETERS INDEPENDENT FROM PRODUCT AGE)

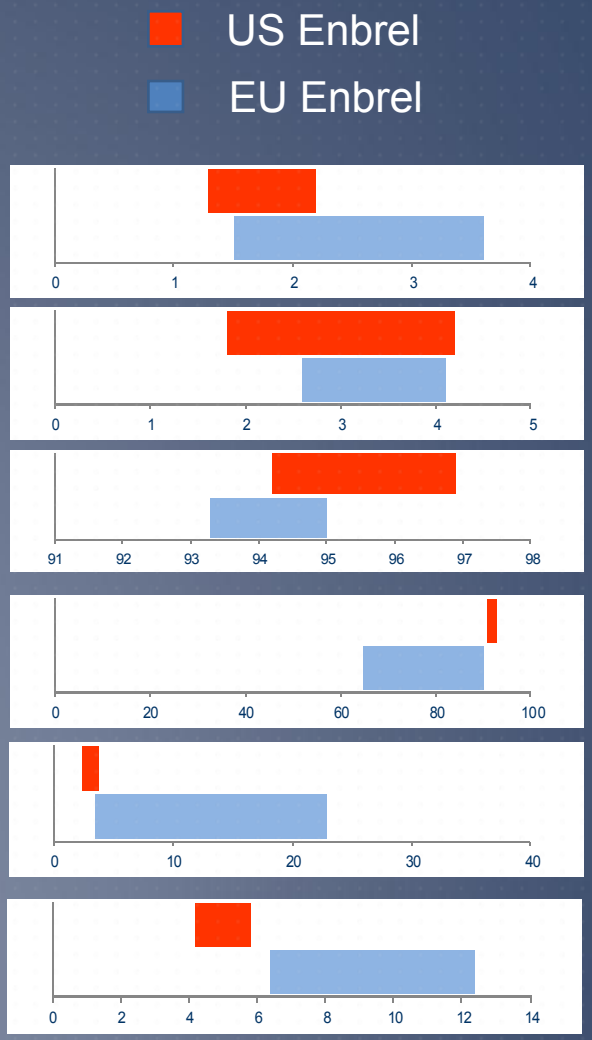
Attribute	Quality Attribute	Enbrel DP Post-shift range	Enbrel DP Post-shift range
Glycosylation	**bGX(-F) [%]**	20.3 – 22.4 (N=10)	20.5 – 22.5 (N=19)
	Alpha-Gal [%]	0.2 – 0.5 (N=13)	0.0 – 0.6 (N=19)
	Man5 [%]	2.7 – 3.8 (N=13)	1.8 – 3.3 (N=19)
Purity	**Proline amide [%]**	1.2 - 3.5 (N=13)	1.5 - 3.7 (N=17)
	Acidic variants (CEX) [%]	0 - 7.5 (N=13)	0 - 8.4 (N=19)
	Basic variants (CEX) [%]	49.5 - 54.2 (N=13)	42.2 - 53.4 (N=19)
Potency	**TNF-alpha RGA [%]**	81 – 94 (N=4)	82 – 106 (N=13)



bGX(-F) = afucosylated complex N-glycans
Alpha-Gal = α-1,3-galactosylated complex N-glycans

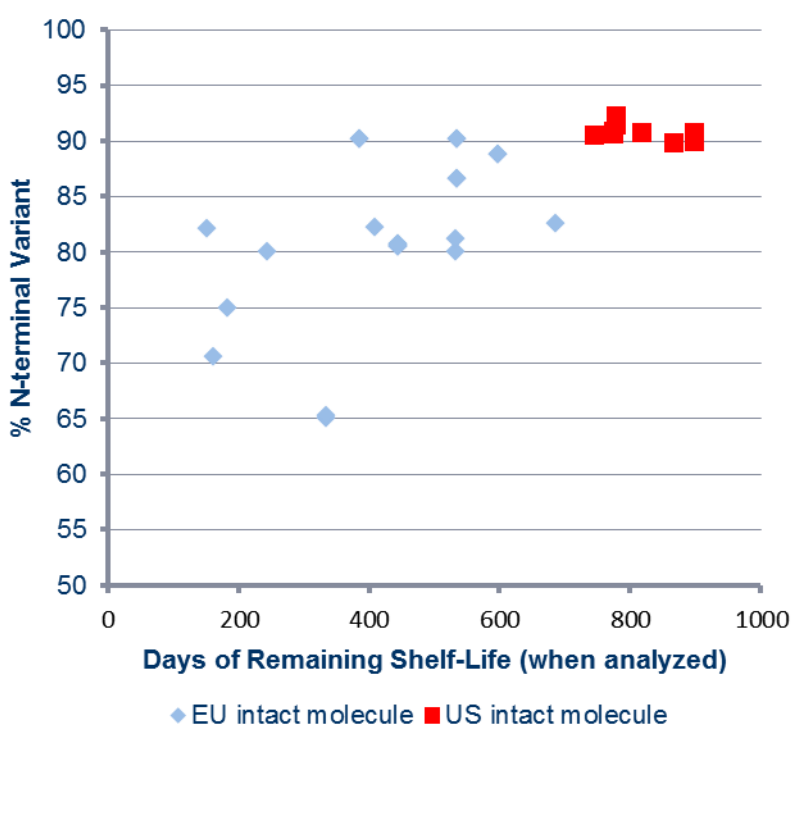
EU AND US ENBREL ANALYTICALLY INDISTINGUISHABLE (PARAMETERS ARE DEPENDENT ON PRODUCT AGE)

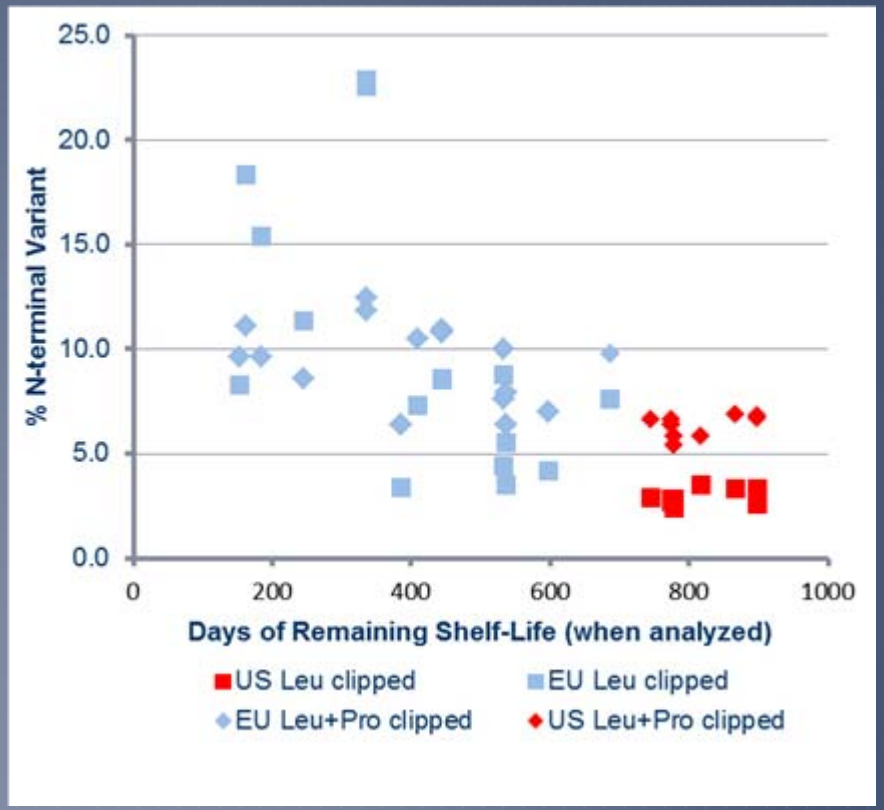
Attribute	Quality Attribute	Enbrel DP Post-shift range	Enbrel DP Post-shift range
Purity	**Aggregates [%] (SEC)**	1.3-2.2 (N=13)	1.5-3.6 (N=18)
	Degradation / Fragmention [%] (SEC)	1.8-4.2 (N=13)	2.6-4.1 (N=18)
	Purity main Peak (SEC) [%]	94.2-96.9 (N=13)	93.3-95.0 (N=18)
Clipping - N-terminal heterogeneity	**L1(1-34) [%] Intact molecule**	90.8-92.7 (N=6)	65.0-90.2 (N=13)
	L1(2-34) [%] N-term. Leu clipped	2.4-3.8 (N=6)	3.4-22.9 (N=13)
	L1(3-34) [%] N-term. Leu+Pro	4.2 - 5.8 (N=6)	6.4 - 12.4 (N=13)



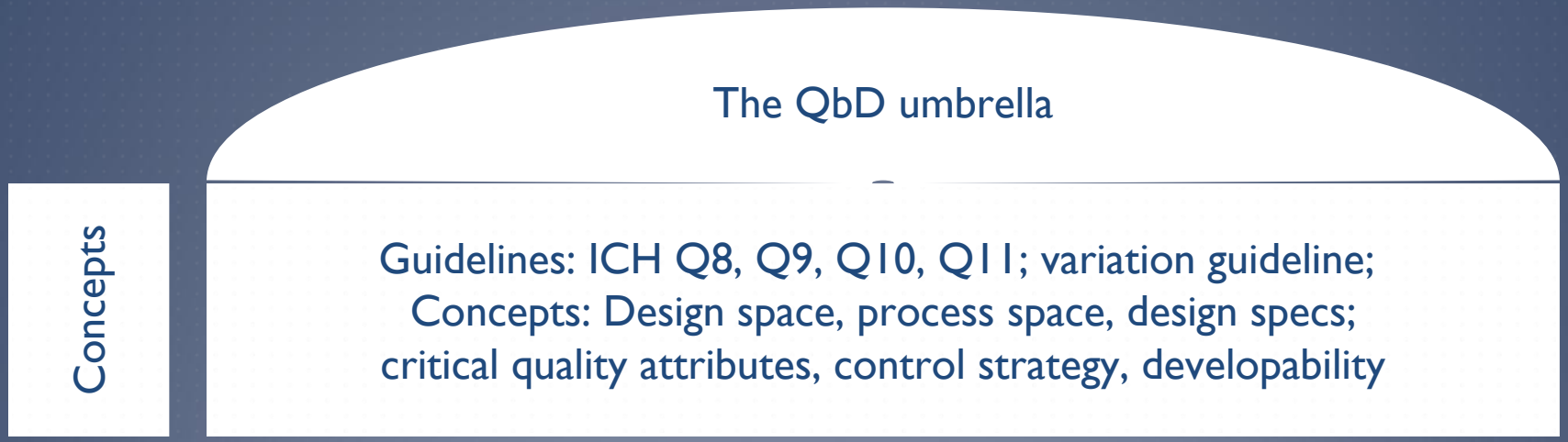
CLIPPING OF N-TERMINUS OF ETANERCEPT IS CORRELATED WITH AGE OF PRODUCT

- Age decreases purity and increases clipping
- Age explains the current non-overlapping data

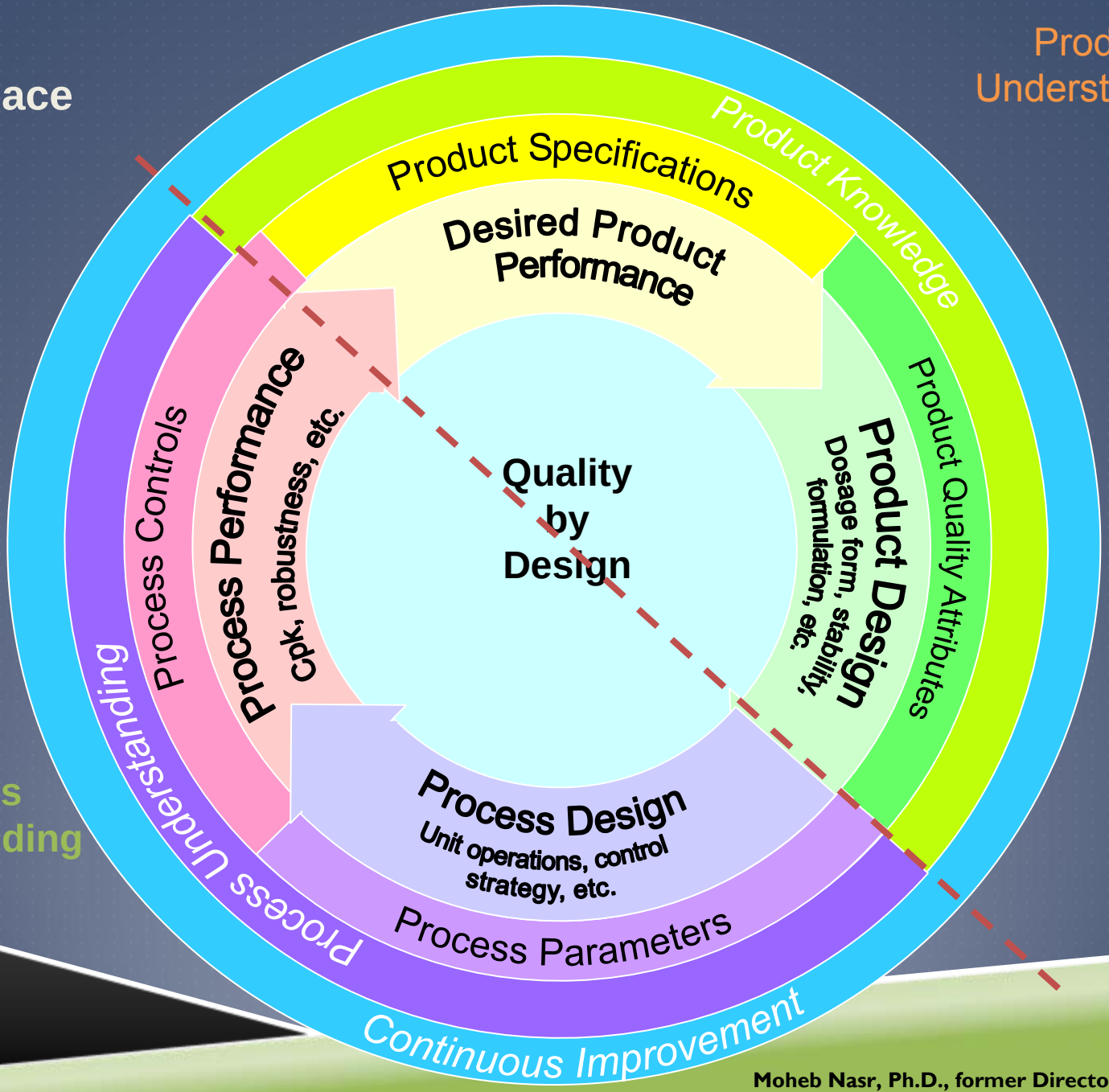




QUALITY BY DESIGN PROCEDURES – DIRECTLY APPLICABLE TO BIOSIMILARS



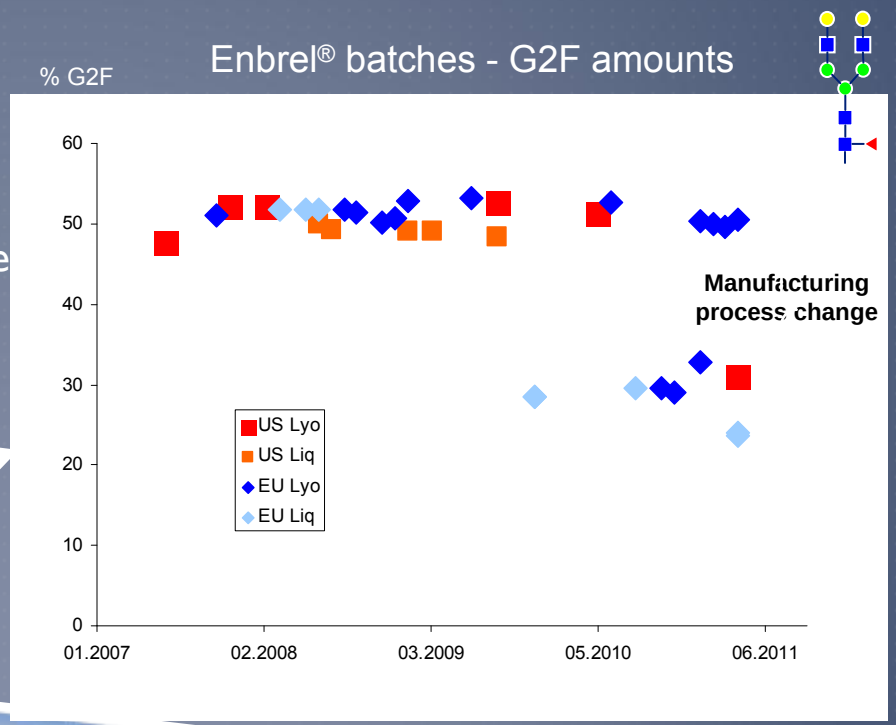
ICH Q8
Design space



QbD Biosimilar Product Specifications Impacted by Variability in Originator Product

- Analytical methods are sensitive to differentiate between
  - Batch to batch
  - Batches before and after a change of the manufacturing process
  - Batches from different sites

- Analytical methods can determine whether batches sourced in different countries are identical or not
  - Microheterogeneity of protein structure
    - Purity profiles
    - Glycan distribution



Schiestl, M. *et al.*, *Nature Biotechnology* 29, 310-312, 2011)

WHAT DOES FDA MEAN? PART II

U.S. Food and Drug Administration
Protecting and Promoting Public Health
www.fda.gov

Fingerprinting

- A subset of information from a complex structure allows identification
  - Allows for extrapolation of attributes that are not measured

Used to identify a single member of a population

- Can this strategy be used for a population or distribution?
- Enoxaparin (a drug product)

Used when members of a group are manufactured using same process (e.g. embryogenesis & growth)

- Will this only work when processes are highly defined like enoxaparin?
- Are biotech manufacturing processes too variable and limited to allow for such an approach for our products?

Slide from Steve Kozlowski at APEC 2012

FINGERPRINT MABS/FUSION PROTEINS AS FDA MIGHT SEE IT

Primary structure e.g.:
LC-MS intact mass
LC-MS subunits
Peptide mapping

Impurities e.g.:
CEX, cIEF acidic and basic variants
LC glycation
Peptide mapping deamidation, oxidation, mutation, glycation
SEC/FFF/AUC aggregation

Biological activity e.g.:
Binding assay
ADCC assay
CDC assay

Higher order structure e.g.:
NMR
CD spectroscopy
FT-IR

PTMs e.g.:
NP-HPLC-(MS) N-glycans
AEX N-glycans
MALDI-TOF N-glycans
HPAEC-PAD N-glycans
MALDI-TOF O-glycans
HPAEC-PAD sialic acids
RP-HPLC sialic acids

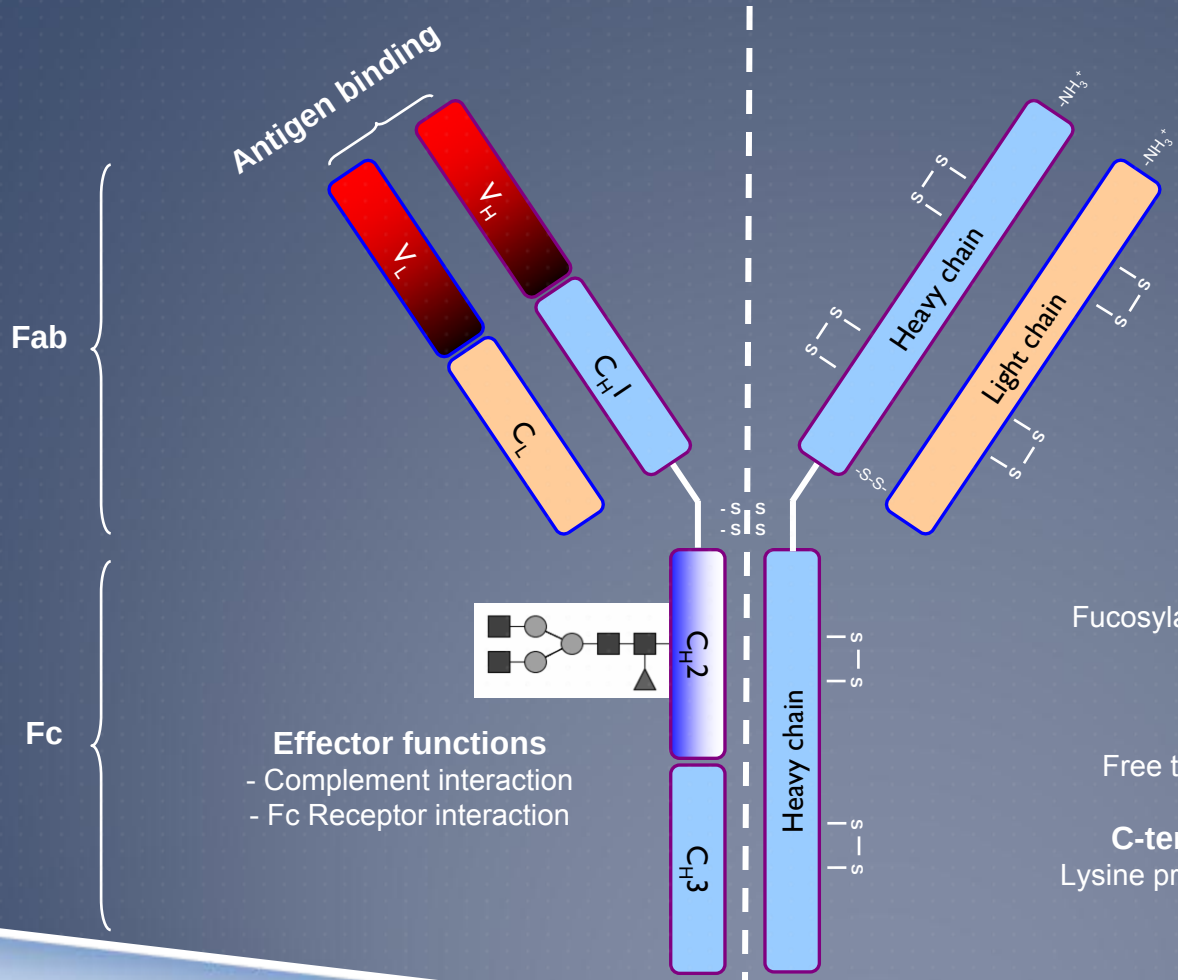
Combination of attributes e.g.:
MVDA, mathematical algorithms

A comprehensive set and combination of orthogonal analytical methods revealing structure-function relationships, delivering in depth comparability information and allowing extrapolation towards non-measured attributes

MABS ARE COMPLEX … BUT CAN BE THOROUGHLY CHARACTERIZED USING STATE-OF-THE-ART ANALYTICS

Biological characteristics

Physicochemical characteristics



Effector functions
- Complement interaction
- Fc Receptor interaction

N-terminal heterogeneity
Pyroglutamate formation
Other modifications

Amino acid modifications
Deamidation, Oxidation, Glycation, Isomerization

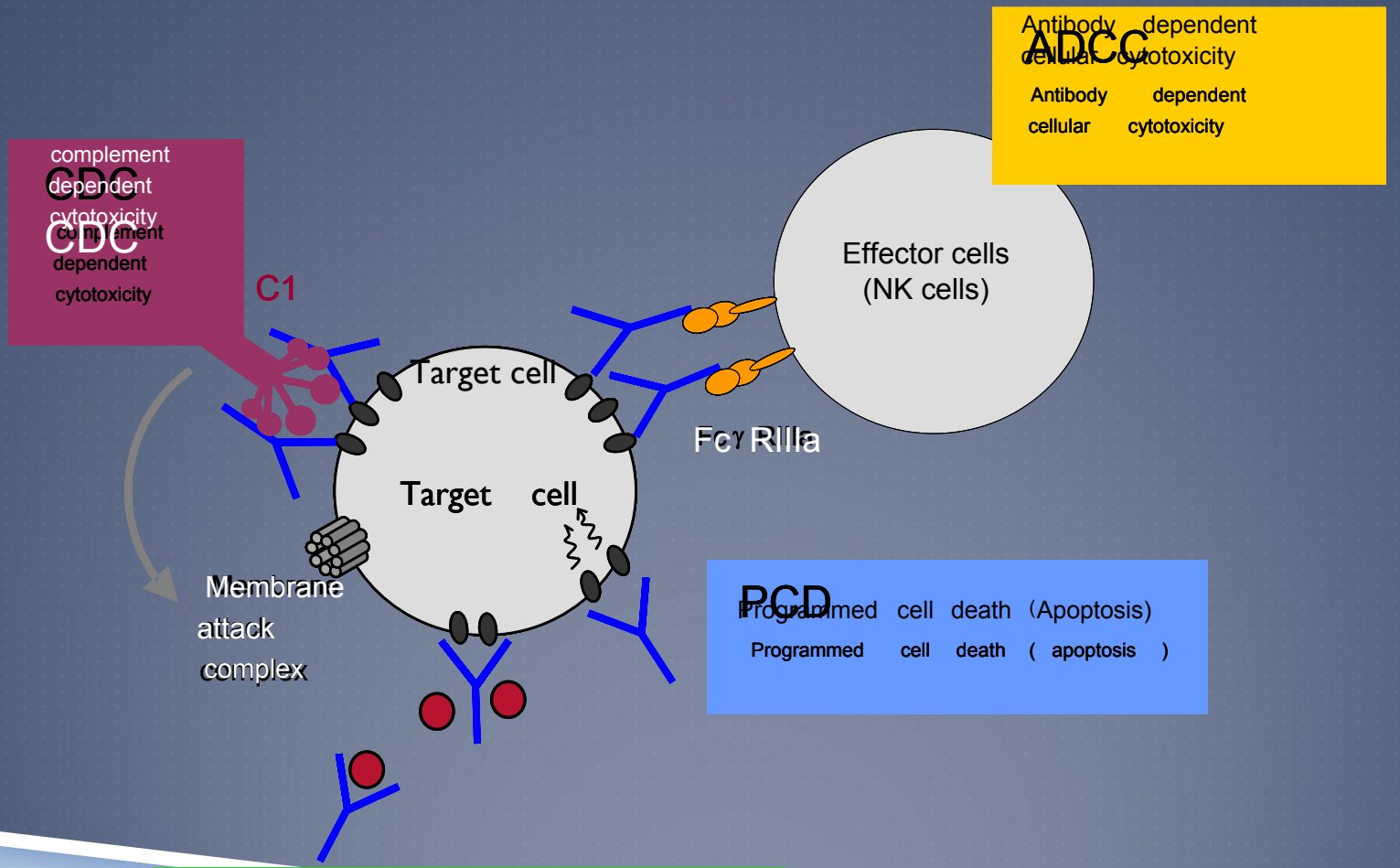
Fragmentation
Cleavage in hinge region, Asp-Pro

Oligosaccharides
Fucosylation, Sialylation, Galactosylation,...

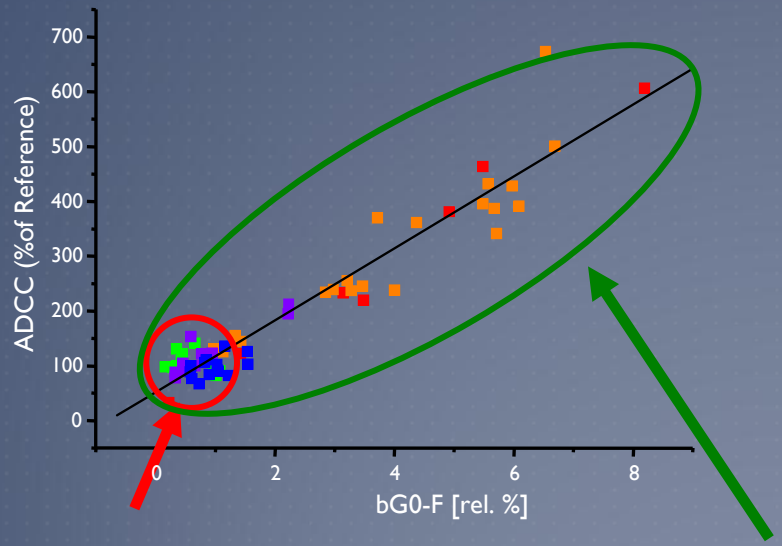
Disulfide Bonds
Free thiols, disulfide shuffling, thioether

C-terminal heterogeneity
Lysine processing, Proline amidation

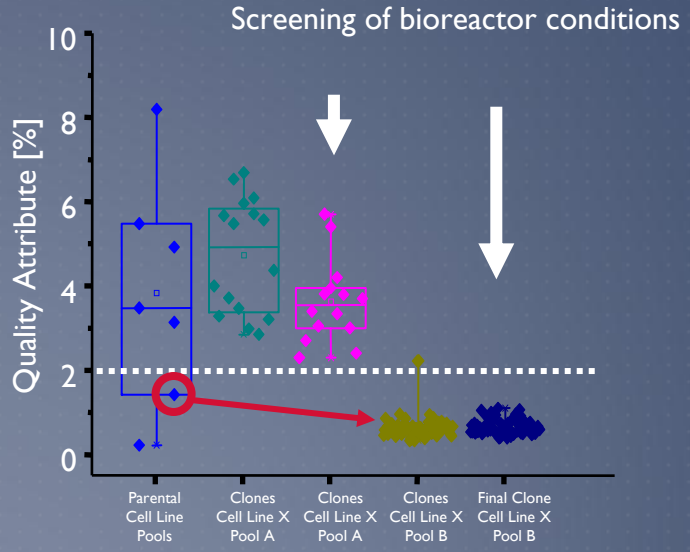
ORTHOGONAL BIOASSAYS ADDRESSING MULTIPLE FUNCTIONS



STRUCTURE FUNCTION RELATIONSHIPS REFINED IN BIOSIMILAR DEVELPOPMENT: ADJUSTING ADCC IN CLONE SELECTION



Range of orginator on market too narrow to deduce S/F-relationship



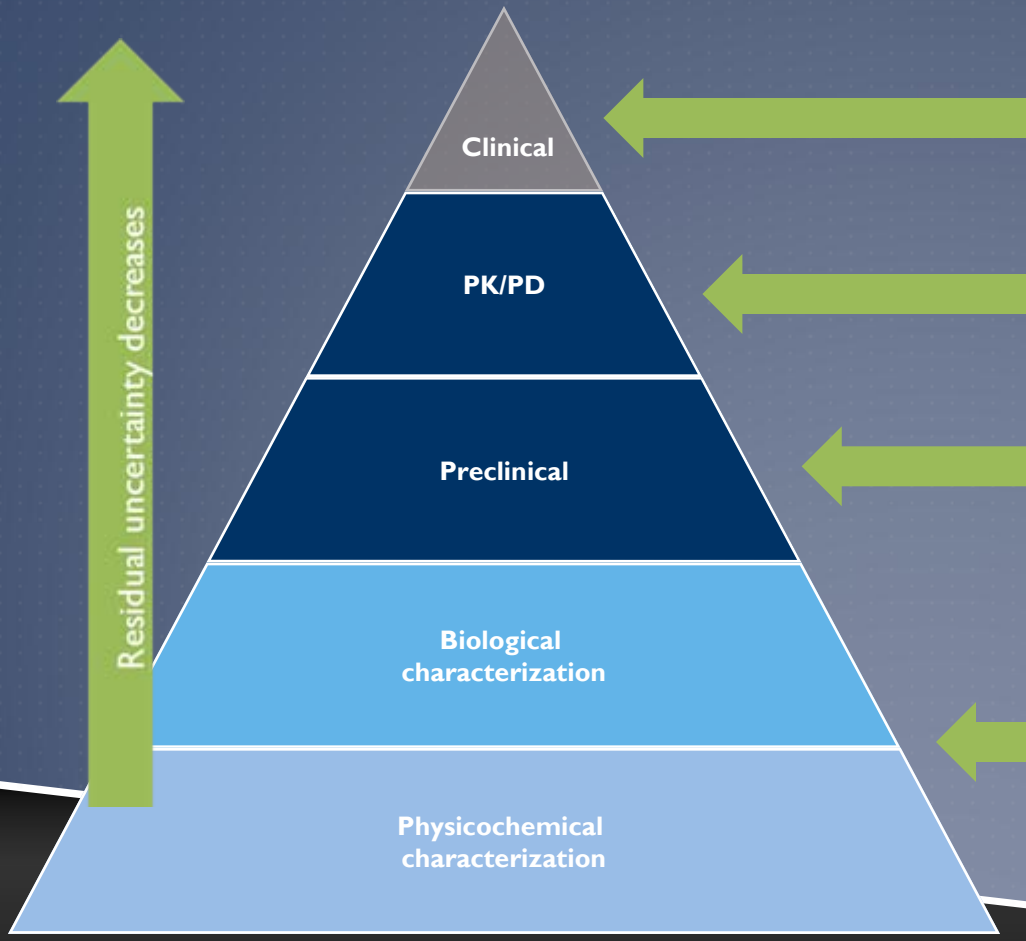
Variability observed during cell line development enables elucidation of quantitative S/F-relationship

OVERVIEW

- Why biosimilars?
- Scientific approach to biosimilar development
- **Abbreviated clinical trial designs**
- Successful commercialization broadens patient access

OVERVIEW OF FDA APPROACH TO BIOSIMILARITY

TOTALITY OF EVIDENCE, STEPWISE, AND RISK BASED APPROACH



Scope and magnitude depends on extent of residual uncertainty from below steps
- No need to independently establish safety or efficacy
- Immunogenicity data is minimally expected

PK and PD (where there is a relevant PD measure) studies are generally expected

Flexibility regarding need for animal studies
- Animal toxicity studies may not be warranted
- Useful if safety uncertainties remain before first-in-man studies

Analytical characterization is the foundation
The more comprehensive and robust the data, the stronger the justification for selective and targeted approach to animal and human testing

Understanding of reference product is important: MOA, SAR, clinical knowledge, availability of clinically relevant PD measure, etc.

USING GCSF AS AN EXAMPLE: PHYSICOCHEMICAL COMPARABILITY

Molecular Attribute	Methods	Zarzio®	Reference Product	International Standard
Composition, Primary Structure	**Peptide map (LC-MS), Peptide Mass Fingerprint (MALDI-MS), MALDI-TOF, Sequencing**	✓	✓	✓
Higher-order Structure, Conformation	**Far and Near UV CD Spectroscopy, Thermal Stability, NMR, SPR, ELISA**	✓	✓	✓
Polarity, Charge, Isoforms	**RP-HPLC, CZE**	✓	✓	✓
Size, Aggregates, Physical Conditions	**SDS-PAGE/Coomassie, SEC, AF4, AUC**	✓	✓	✓
Binding	**Cell Assays, SPR, ELISA**	✓	✓	✓
Biological Activity	**Cell Assays, In-Vivo Assay**	✓	✓	✓

NB : Fligrastim is a non-glycosylated protein thus much easier to characterise proving physicochemical equivalence

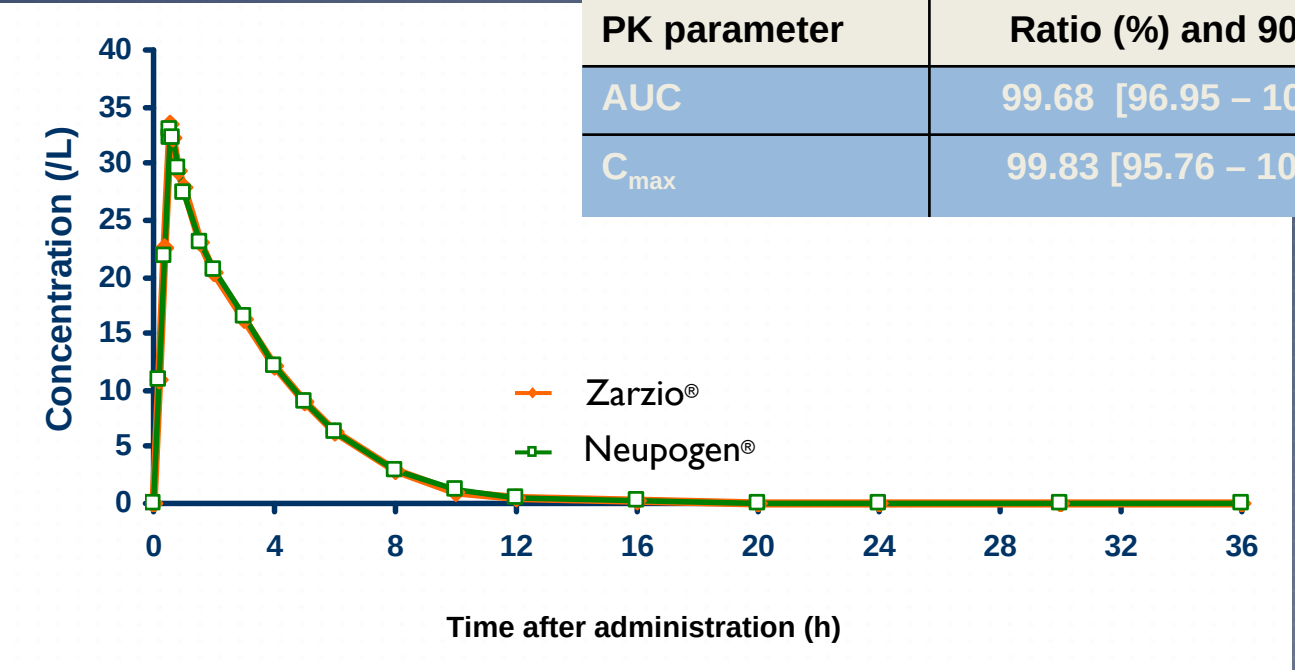
MULTIPLE PHASE I STUDIES CONFIRM BIOEQUIVALENCE

Study	EP06-101	EP06-102	EP06-103	EP06-105
Type of study	Randomized, double-blind, 2-way crossover	Randomized, double-blind, 2-way crossover	Randomized, double-blind, 2-way crossover, with two dose groups	Randomized, double-blind, 2-way crossover
Study population	Healthy volunteers	Healthy volunteers	Healthy volunteers	Healthy volunteers
Number of subjects	40	26	56	24
Age range of volunteers Sex/race distribution	Age range: 25-45 years Race: 100% Caucasian Sex distribution: 52.5% male and 47.5% female	Age range: 23-39 years Race: 100% Caucasian Sex distribution: 54% male and 46% female	Age range: 21-54 years Race: 100% Caucasian Sex distribution: 59% male and 41% female	Age range: 21-53 years Race: 100% Caucasian Sex distribution: 54% male and 46% female
Dose	10 µg/kg	5 µg/kg	2.5 or 5 µg/kg	1 µg/kg
Frequency of dosing	Multiple s.c. injections for seven days	Single i.v. injection	Multiple s.c. injections for seven days	Single s.c. injection
Objectives	Primary: Evaluate PK bioequivalence Secondary: Compare PD, safety, local tolerance	Primary: Evaluate PK bioequivalence Secondary: Compare PD and safety	Primary: Evaluate PD equivalence Secondary: Safety, local tolerance, PK	Primary: Evaluate PD equivalence Secondary: Safety, local tolerance, PK

Four randomized, double-blind, single and multiple dose, crossover studies using doses from 1 to 10 µg/kg body weight were conducted in 146 healthy female and male subjects.

European Public Assessment Report (EPAR)
http://www.emea.europa.eu/humandocs/PDFs/EPAR/ilgrastimHexal/H-918-en6.pdf

PHASE I: STUDY EPO6-102 PK RESULTS



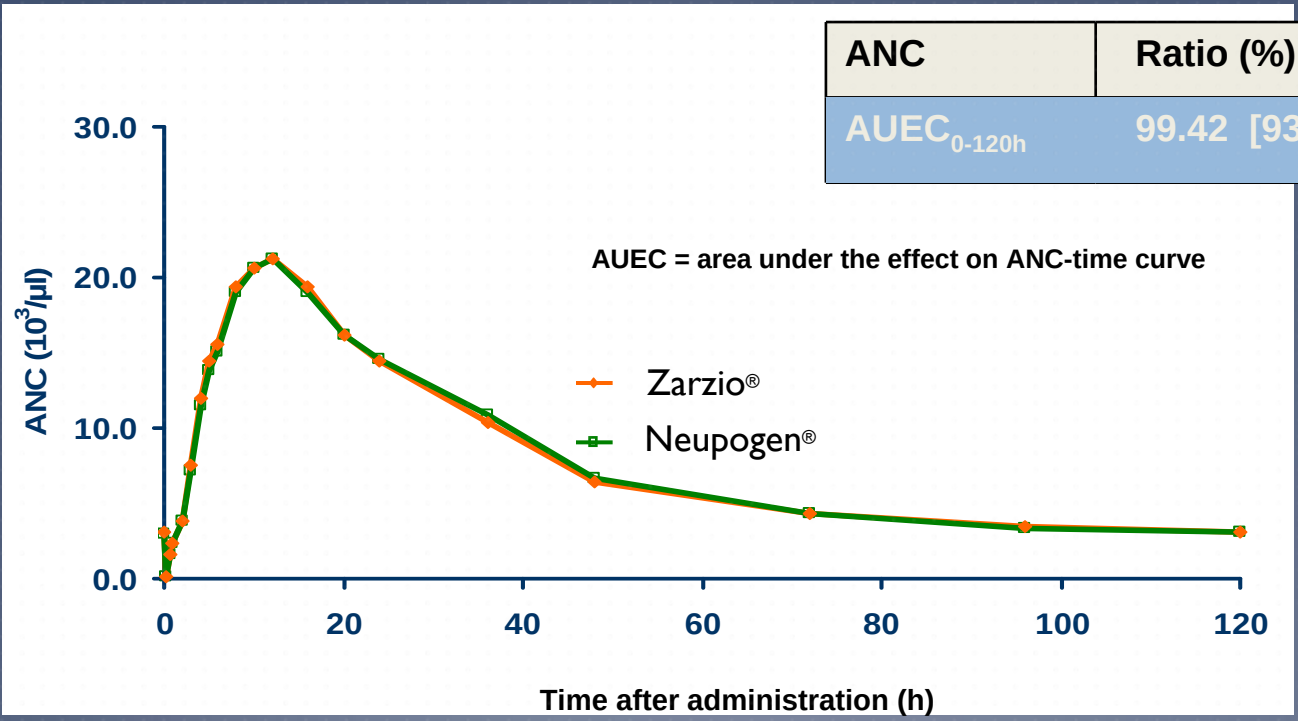
PK parameter	Ratio (%) and 90% CI
AUC	99.68 [96.95 – 102.47]
C_{max}	99.83 [95.76 – 101.98]

- Dose: 5 µg/kg IV single-dose
- Curves superimposable for Zarzio® and Neupogen®
- Zarzio® and Neupogen® show bioequivalence after a single IV dose

Gascon P et al. *Ann Oncol*, in press

PHASE I: STUDY EPO6-102 PD RESULTS

ANC	Ratio (%) and 95% CI
$AUEC_{0\text{-}120h}$	99.42 [93.53 – 105.70]

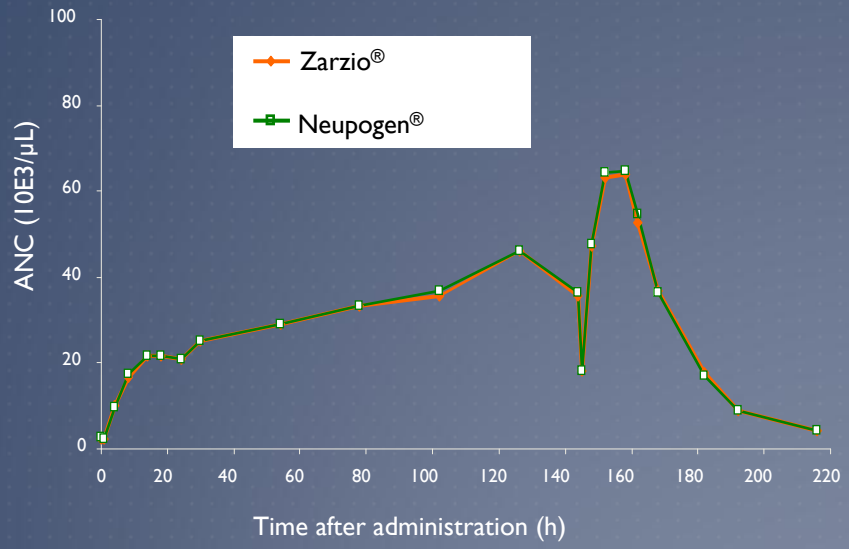


- Dose: 5 µg/kg IV single-dose
- ANC curves superimposable for Zarzio® and Neupogen®
- Zarzio® and Neupogen® show comparable pharmacodynamics after a single IV dose

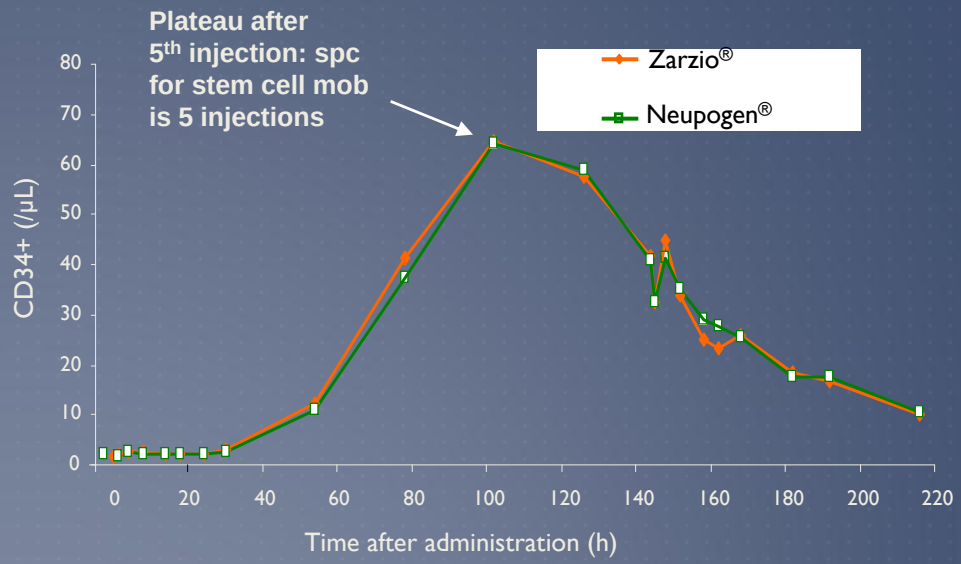
Gascon P et al. *Ann Oncol*, in press

PHASE I: STUDY EPO6-101 PD RESULTS

Development of
absolute neutrophil count (ANC)



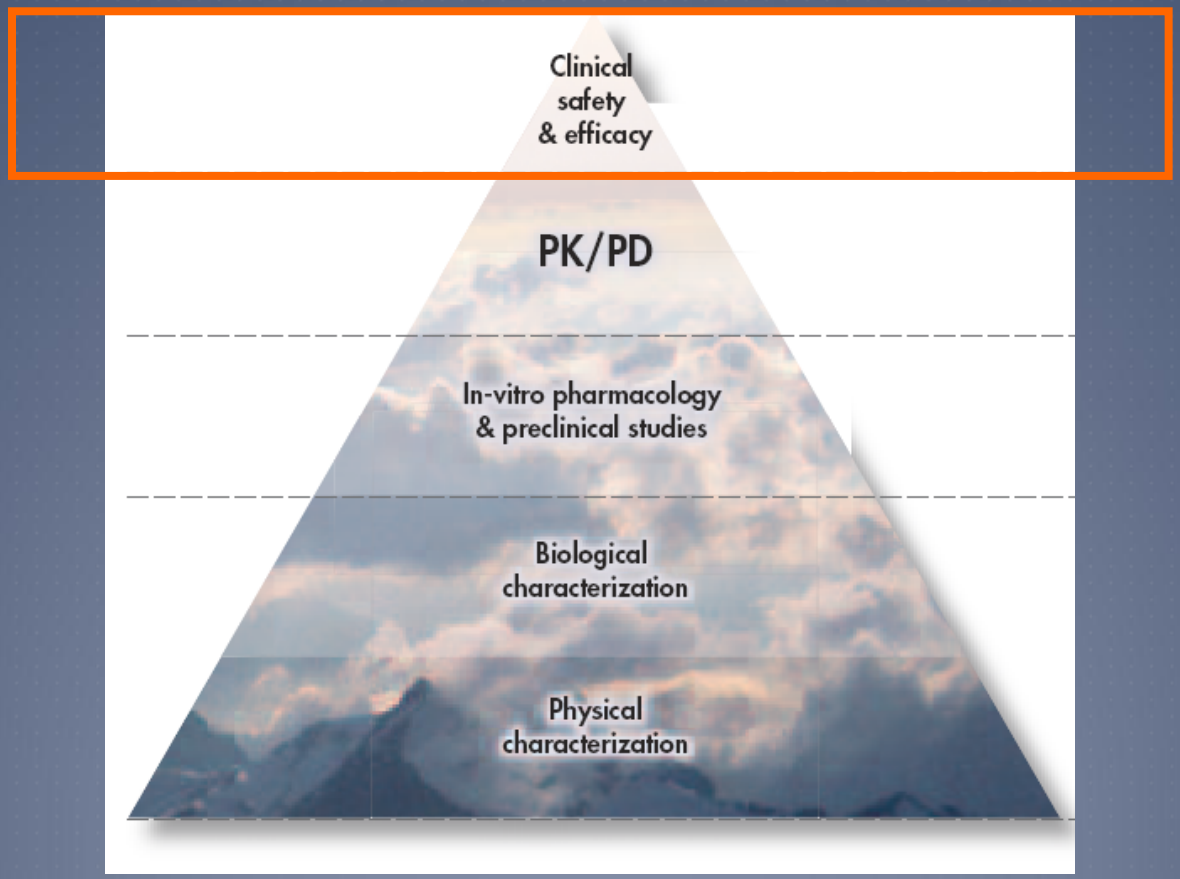
Development of
CD34⁺ cells



- Dose: 10 µg/kg SC for 7 days
- CD34⁺ count = surrogate marker for efficacy in stem cell mobilisation
- Curves for both ANC and CD34⁺ cells superimposable for Zarzio® and Neupogen®

Gascon P et al. *Ann Oncol*, in press

PK/PD BE DEMONSTRATION IS PIVOTAL: WHAT IS NECESSARY TO CONFIRM EFFICACY AND SAFETY



PHASE III STUDY EP06-301

Design

- Open, single-arm, multi-center study evaluating the safety and efficacy of EP2006 in breast cancer patients
- n = 170 chemotherapy-naïve patients with high risk stage II or stage III/IV breast cancer
- Chemotherapy: 4 cycles of *doxorubicin (60 mg/m^2) and docetaxel (75 mg/m^2) every 3 weeks
- EP2006 was administered (30 MUs <60kg, 48 MUs >60kg) from day 2 of each cycleANC reached 10 x 10^9/l post nadir or for up to 14 days

Main criteria for evaluation of safety

- Incidence, occurrence and severity of adverse events
- Detection of anti-rhG-CSF antibody formation

Main criteria for evaluation of efficacy

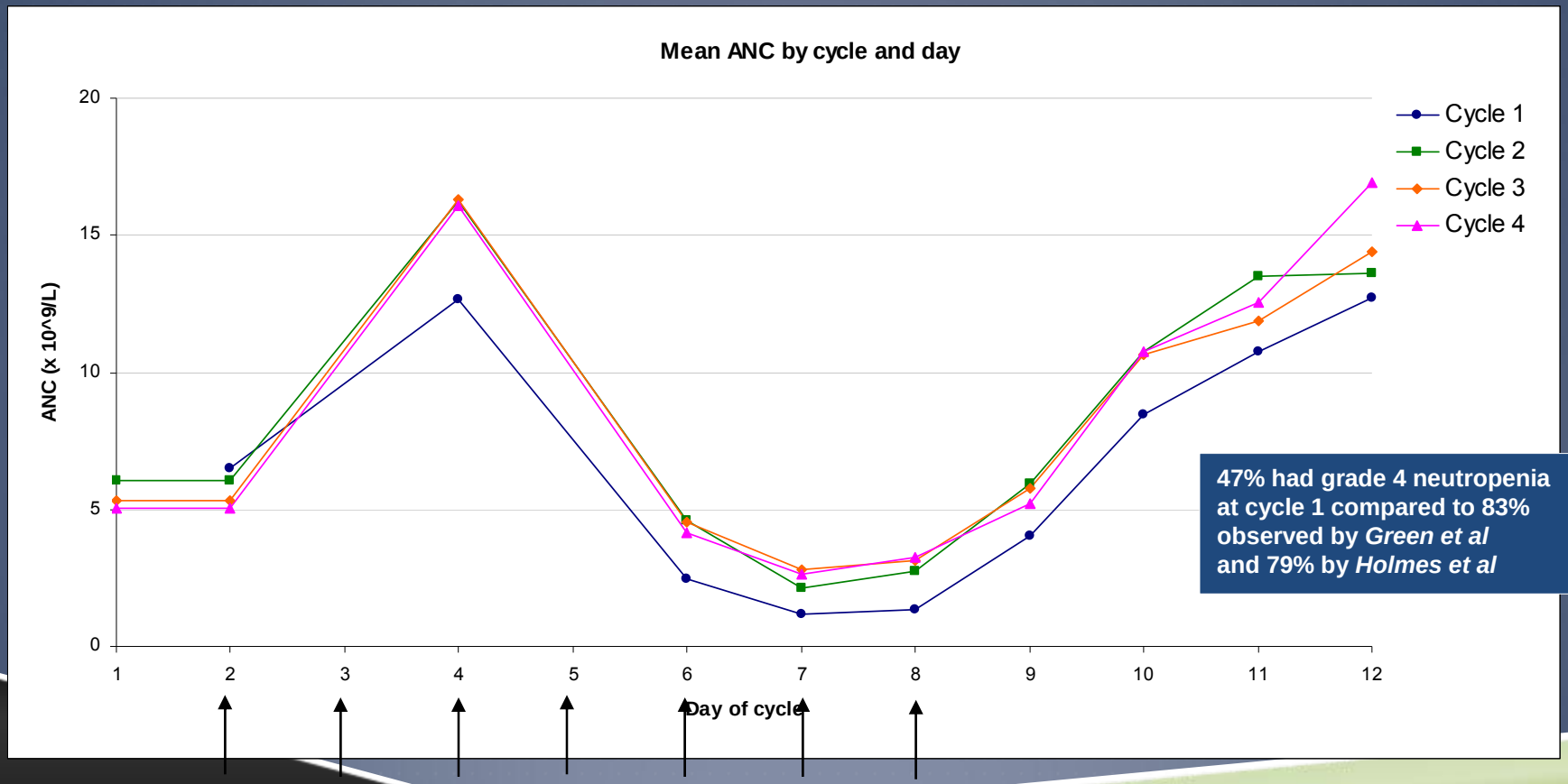
- Incidence and duration of grade 4 neutropenia
- Incidence of febrile neutropenia

***** EORTC 2006 rate as 40% risk of febrile neutropenia

PHASE III STUDY: EFFICACY

Mean ANC curve for each cycle

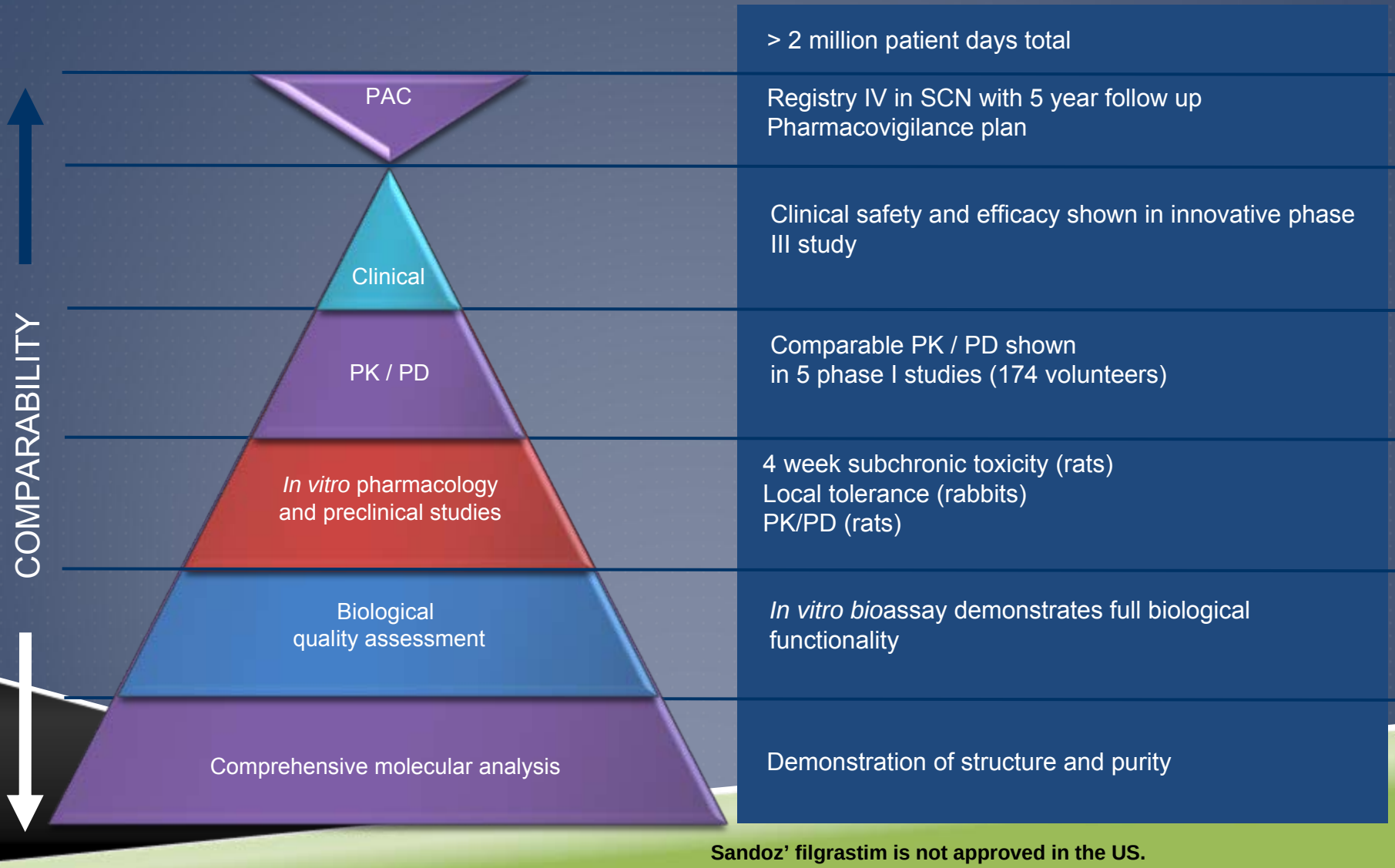
Typical to see lowest nadir following cycle 1



47% had grade 4 neutropenia at cycle 1 compared to 83% observed by *Green et al* and 79% by *Holmes et al*

ANC : Healthy 3-5 x 10^9, grade 4 CIN 0.5 x 10^9, grade 3 CIN 1 x 10^9, grade 2 CIN 1.5-1 x 10^9

SANDOZ FILGRASTIM - SUMMARY OF CLINICAL EXPERIENCE



Sandoz' filgrastim is not approved in the US.

INNOVATION REQUIRED IN BOTH TECHNICAL DEVELOPMENT AND CLINICAL DEVELOPMENT

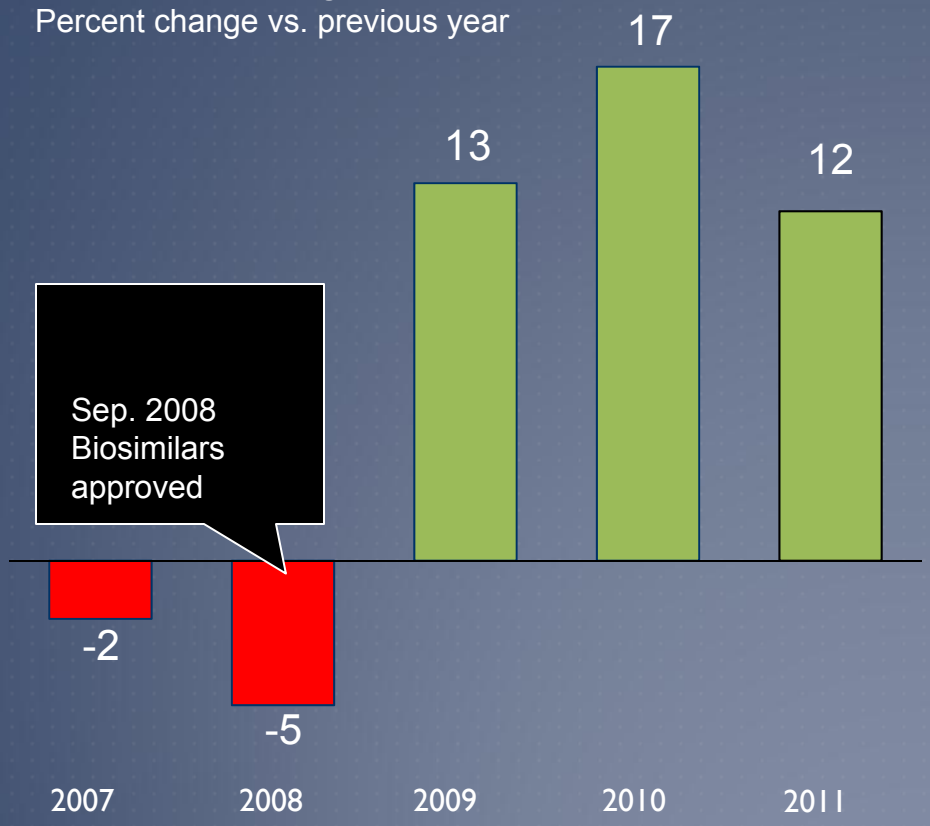
	Key challenges
Time & Investment	• **Significant expense** (USD 100 - 250m) • **Long time** to develop (7-8 years)
Technical Development	• **Achieving "highly similar"** to match originator molecule profile • **Matching** final dosage form of originator
Clinical Development	• **Use of novel endpoints and populations** to confirm biosimilarity (not *de novo* safety/efficacy) • **Clinical trial design** to support extrapolation across indications, interchangeability & commercial success

Overview

- Why biosimilars?
- Scientific approach to biosimilar development
- Abbreviated clinical trial designs
- **Successful commercialization broadens patient access**

UK EXAMPLE: BIOSIMILARS EXPAND ACCESS TO G-CSF[1]

UK G-CSF volume growth
Percent change vs. previous year



Sandoz' filgrastim is not approved in the US.

- **G-CSF prevents hospital re-admissions** due to infections
- **Many physicians have moved G-CSF back to 1st-line cancer treatment** due to lower biosimilars cost
- **Sandoz's filgrastim (G-CSF) "Patient Support Kits"** expand patient access:
  - Patients self-administer at home
  - Substantial efficiency savings

[1] Granulocyte colony stimulating factor

SOURCE: IMS, NHS